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ORIGINAL ARTICLE

Diagnosis, Prognosticators, and Management of Acute Invasive Fungal Rhinosinusitis: Multidisciplinary Consensus Statement and Evidence-Based Review with Recommendations

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Abstract

Background: Acute invasive fungal sinusitis (AIFS) is an aggressive disease that requires prompt diagnosis and multidisciplinary treatment given its rapid progression. However, there is currently no consensus on diagnosis, prognosis, and management strategies for AIFS, with multiple modalities routinely employed. The purpose of this multi-institutional and multidisciplinary evidence-based review with recommendations (EBRR) is to thoroughly review the literature on AIFS, summarize the existing evidence, and provide recommendations on the management of AIFS.

Methods: The PubMed, EMBASE, and Cochrane databases were systematically reviewed from inception through January 2022. Studies evaluating management for orbital, non-sinonasal head and neck, and intracranial manifestations of AIFS were included. An iterative review process was utilized in accordance with EBRR guidelines. Levels of evidence and recommendations on management principles for AIFS were generated.

Results: A review and evaluation of published literature was performed on 12 topics surrounding AIFS (signs and symptoms, laboratory and microbiology diagnostics, endoscopy, imaging, pathology, surgery, medical therapy, management of extrasinus extension, reversing immunosuppression, and outcomes and survival). The aggregate quality of evidence was varied across reviewed domains.

Conclusion: Based on the currently available evidence, judicious utilization of a combination of history and physical examination, laboratory and histopathologic techniques, and endoscopy provide the cornerstone for accurate diagnosis of AIFS. In addition, AIFS is optimally managed by a multidisciplinary team via a combination of surgery (including resection whenever possible), antifungal therapy, and correcting sources of immunosuppression. Higher quality (i.e., prospective) studies are needed to better define the roles of each modality and determine diagnosis and treatment algorithms.

KEYWORDS
antifungals, aspergillosis, fungus, immunosuppression, intracranial, invasive fungal sinusitis, management, mucormycosis, orbit, outcomes, surgery, survival

1 | INTRODUCTION

Fungal infections of the paranasal sinuses can occur on a spectrum ranging from indolent to fatal. In the latter case, termed invasive fungal sinusitis (IFS), fungal organisms, which are ubiquitous in the environment, invade the sinonasal epithelium, bone, and the vasculature, thereby causing local necrosis and infarction of tissues, with subsequent spread of fungus to other areas. IFS primarily occurs in immunocompromised patients; a study of over 800 IFS patients reported that the predominant underlying comorbidities were types 1 and 2 diabetes (47.8%) and hematologic disorders (39.8%).[1,2] The literature has described the most common pathogens as *Aspergillus* (69%), followed by *Mucormycetes* (22%), *Cryptococcus* spp (4%), and *Fusarium* spp (2%).[3] IFS can be classified into acute IFS (AIFS) or chronic IFS (CIFS), with AIFS having a more aggressive course and CIFS with a more indolent course. AIFS necessitates early diagnosis and consideration for urgent intervention, given a high mortality rate (50%).[4] This provides a challenge to clinicians because symptoms of AIFS can range from asymptomatic to mild symptoms, including facial swelling, fever, and nasal congestion, to late-stage findings, such as ophthalmoplegia, vision loss, proptosis,

and stroke.[4–8] As these symptoms vary and are nonspecific, diagnostic testing is paramount to the diagnosis of AIFS.

There is currently no consensus on the diagnostic algorithm for AIFS, with surrounding controversy given limited high-quality evidence and varying protocols across multiple centers and consortia. Furthermore, as a disease process managed in a multidisciplinary fashion (otolaryngology, infectious disease, ophthalmology, neurosurgery, transplant medicine), each specialty has unique perspectives regarding this condition, which may not overlap across disciplines. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) describes the two most important diagnostic criteria for AIFS as rhinosinusitis confirmed by radiologic imaging or showing tissue destruction, and histopathologic evidence of fungal invasion into mucosa, submucosa, blood vessels, or bone.[2] The International Consensus Statement in Allergy and Rhinology: Rhinosinusitis (ICAR) suggests that imaging studies including computed tomography (CT) can be used to demonstrate mucoperiosteal thickening within the nasal cavity, whereas magnetic resonance imaging (MRI) may demonstrate bone erosion or orbital/intracranial involvement. The statement also describes the use of histology with frozen sections and nasal endoscopy as being critical with findings such as edema with violaceous or pale mucosa, insensate mucosa, or necrosis of the mucosa being indicative of AIFS.[1] Last, the consensus statement from Infectious Diseases Society of America (IDSA) states that the criteria for proven invasive fungal disease include histopathologic, cytopathologic, or direct microscopic examination of hyphae, recovery of fungus by culture from a sterile site, blood cultures yielding fungus, serology for fungal antigens if applicable, and amplification of fungal DNA by polymerase chain reaction (PCR) if applicable.[9] There is increasing evidence that radiologic imaging of AIFS is more varied than previously described, and the IDSA statement suggests that high-resolution CT scan is preferred over other imaging modalities due to the increased sensitivity, availability, and experience with interpretation.[9] As evident in the varying diagnostic criterion across evidence provided from multiple specialties, there is limited consensus on the diagnosis of AIFS.

In addition, there is controversy surrounding the treatment of AIFS, given limited high-quality evidence governing disease management, varying protocols across multiple centers and consortia, and the multidisciplinary expertise required for treatment. Currently, in the literature, both the EPOS and the ICAR suggest that the mainstay treatments for AIFS include surgical debridement, initiation of antifungal therapy, and reversal of immunosuppression.[1,2] In the case of surgical intervention, studies have shown that the odds of mortality are decreased in patients who underwent endoscopic or open surgery for AIFS.[4] However, there is a lack of literature and guidelines regarding the extent of resection required, the role of extended surgical approaches, open vs. endoscopic vs. combined approaches, or repeat resections after initial treatment. In the case of antifungal therapy, there is consensus that empiric systemic antifungals should be started in confirmed AIFS.[1,2,10] However, there is ongoing discourse regarding the use of preemptive antifungal therapy in high-risk patients, length of antifungal therapy, and choice of antifungals.[10] Depending on the suspected fungal organism, amphotericin B, azoles, and caspofungin have all been shown to be efficacious in reducing mortality.[1,2,10] In addition to systemic therapy, it has also been reported that transcutaneous retrobulbar injections of amphotericin B have been used with varying success in managing fungal invasion into the orbit.[2] With regard to reversing immunosuppression, multiple guidelines recommend reversal of the underlying immunodeficiency, but there is currently no guidance on treatment options.[1,10] The Recommendations of the Infectious Diseases Working Party state that colony-stimulating factors and granulocyte transfusions may be considered in selected patient populations on a case-by-case basis, but the limited literature on the topic has been mixed.[2,10]

To date, there are currently no evidence-based recommendations on the diagnosis, prognosis, and treatment of AIFS. Previous documents have described the mainstay diagnosis, prognosis, and treatments for AIFS, and many of the recommendations remain expert opinion at best. The purpose of this multidisciplinary consortium and document is to thoroughly review the literature on AIFS; summarize the existing evidence; and provide recommendations on the diagnosis, prognosis, and management of AIFS.

2 | MATERIALS AND METHODS

The development of this article was performed using the following methodology for an evidence-based review with recommendations (EBRR).[11] A group of multidisciplinary authors spanning multiple institutions with clinical and academic expertise in the diagnosis, prognosis, and management of AIFS was recruited. Authors with expertise in IFS were selected as senior authors for each section. Authors conducted a systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and using the following databases: Ovid MEDLINE (1947–present), EMBASE (1974–present), and Cochrane Reviews databases. Studies evaluating modalities of diagnosis, prognosis, and management for orbital, nonsinonasal head and neck, and intracranial manifestations

AIFS were included, with each subsection developed a priori by authors based on extensive review of the literature. Studies that did not include orbital or intracranial manifestations (i.e., limited to sinonasal involvement) were also included. Data from all ages were included given the paucity of literature on this topic. Pulmonary and skin fungal infections, localized and/or noninvasive sinonasal fungal infections (e.g., fungus ball), CIFS, and chronic granulomatous IFS were excluded. Case studies were also excluded. The search terms used for each section included the following query header: "Acute AND (invasive fungal sinusitis OR invasive fungal rhinosinusitis OR IFS)" and relevant additional terms for the specified section (e.g., AND ENDOSCOPY). Studies were evaluated for quality of research methodology and assigned a standard level of evidence based on the 2011 Oxford levels of evidence.[12] During the systematic review process, summary tables of all included studies were developed with the following: study, year of publication, level of evidence, design, study groups, clinical endpoint(s), and conclusion. After evaluation of each included study, an aggregate grade of evidence was produced and recommendations were given based on the American Academy of Pediatrics Steering Committee on Quality Improvement and Management.[13] Recommendations accounted for aggregate level of evidence, as well as the balance of benefit, harm, and costs. These recommendations are summarized at the end of each section and include the authors' benefit–harm assessment and value judgment. Recommendations were compiled for iterative review, in which recommendations were critically evaluated based on the literature per EBRR guidelines.[11] All sections underwent iterative review by two primary editors (L.T.R., I.M.H., C.H.L., or E.C.K.) and were then compiled by the senior author (E.C.K.). Discrepancies in recommendations were raised during the iterative and secondary reviews, and all conflicts resolved between the senior author (E.C.K.) and the author(s) who raised the point. The final draft was then carefully reviewed by all authors and consensus was reached. All authors approved the final document after review of the final submitted draft.

3 | SIGNS AND SYMPTOMS

A high index of suspicion for at-risk patients is important for early diagnosis of AIFS, as the initial symptoms can be nonspecific.[14,15] The variance in reported signs and symptoms is due to stage of disease progression, extent of disease involvement of tissues outside the sinuses and nasal cavity, time to diagnosis,[4] and quality of available data. This can range from virtually no sinonasal symptoms in patients identified close to infection onset to severe symptoms, such as visual impairment, ophthalmoplegia, ptosis, and altered mental status,[16,17] with more widespread disease. Table 1 summarizes the evidence surrounding utilizing signs and symptoms for AIFS diagnosis.

3.1 | Physical signs and subjective symptoms

Among identified studies, there is variability in reporting of symptoms. In some studies, fever was not reported as a separate symptom, as neutropenic fever was the trigger for otolaryngology consultation.[14,24] Other studies combined ophthalmoplegia, diplopia, vision changes, and other ocular symptoms into a category such as "visual dysfunction."[25,55] Similarly, the descriptions of pain (facial, orbital, headache, etc.) are generally heterogeneous.[26,31] A minority of articles did not provide information on symptom prevalence. Despite heterogeneity, there is agreement regarding common signs and symptoms. The highest quality studies, which include signs and symptom prevalence, reported fever (41% to 67% of patients),[3–7,19] facial swelling (41% to 65%),[4,5,7,8] facial pain (29% to 71%),[4–6,8,56] nasal congestion (32% to 52%),[4–7] ophthalmoplegia (17% to 51%),[4,28] vision loss (18% to 68%),[4–6,8,56] and proptosis (13% to 63%)[4,5,8,56] as the most common signs and symptoms.

A broader range of signs and symptoms occurs with varying prevalence when including data from level 4 studies. Presentation can be grouped into general categories of constitutional, sinonasal, otolaryngologic, cranial nerve, and ophthalmologic manifestations. Constitutional symptoms included fever (ranging from 9% to 100% of patients in identified studies),[4,6,15,19,31,48–49,52] headache (25% to 100%),[33–34,43,53] and altered mental status (11% to 27%).[17,45,51] Sinonasal signs and symptoms reported include nasal congestion (14% to 100%),[4,22,48–49,52] nasal crusting/eschar (8% to 90%),[20,36,44,56] rhinorrhea (21% to 66%),[6,19,20] necrotic mucosa (21% to 100%),[28,29,53] and septal perforation/ulceration (9% to 38%).[35,46,51] Other otolaryngologic signs and symptoms identified included facial swelling (27% to 100%),[7,35,47,51] facial/orbital/jaw pain (14% to 86%),[6,21,22,26,35] and palate ulceration (5% to 25%),[20,28,33,35,45] with cough (up to 64%)[53] and trigeminal neuralgia (up to 25%)[32] being noted less frequently.

Cranial nerve symptoms (25% to 49%),[30,33,39,57] including facial anesthesia (8% to 55%),[5,7,15,31,37–38,56,58] palatal anesthesia (up to 8%),[15] and facial paralysis (25% to 44%),[33,47] as well as ophthalmologic symptoms/symptoms, which include loss of visual acuity (26% to 87%),[17,26,30,38] proptosis (16% to 100%),[35,45,47] ophthalmoplegia (17% to 60%),[28,38,42,58] diplopia/extraocular muscle weakness (9% to 50%),[7,24,46,55] and ptosis (up to 100% in some series)[26,35,45] frequently develop if the disease extends outside the sinonasal cavity.

TABLE 1 Signs and symptoms.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Smith[18]	2016	2	Systematic review	Pediatric patients with AIFS (12 studies, 103 patients)	1) Overall survival	Symptoms included fever, orbital involvement, facial pain, edema, rhinorrhea, headache, and nasal obstruction/congestion.
Turner[4]	2013	2	Systematic review	1) SR of level 4 data 2) AIFS patients ($n = 807$)	1) Symptoms 2) Prognostic factors 3) Survival	Overall survival 49.7%; symptoms: facial swelling (64.5%), fever (62.9%), and nasal congestion (52.2%).
Lagos[19]	2021	3	Cohort study	1) 50 immunocompromised patients 2) 9 of 50 with AIFS	1) Symptoms 2) Clinical data 3) Survival	Symptoms included fever, febrile neutropenia, headache, rhinorrhea, pain, nasal obstruction, and decreased visual acuity, and ulceration or necrosis was less frequent.
Alejandro[20]	2020	3	Retrospective cohort	Pediatric patients diagnosed with AIF ($n = 18$)	1) Mortality 2) Etiology of immunosuppression 3) Prognostic factors	Delay of >7 days from diagnosis to surgery was a negative prognostic factor; nasal obstruction was seen in 83%, nasal crusting in 61%, and rhinorrhea in 66% of patients.
Malleshappa[21]	2020	3	Retrospective cohort	Patients with biopsy-proven AIFS ($n = 51$)	1) Frequency of debridement 2) Time to surgery from diagnosis	Symptoms included headache (66.7%), facial pain (54.9%), facial swelling (43.1%), ocular symptoms (51.9%), and periorbital swelling (21.5%).
D'Andrea[22]	2019	3	Retrospective cohort	Patients with skull base AIFS ($n = 14$)	Demographic and clinical data, outcomes	Presenting symptoms included headache (50%), eye pain (42.9%), facial pain (28.6%), visual changes (21.4%), and congestion (14.3%).
Candoni[3]	2019	3	Retrospective cohort	1) Oncohematologic patients with cerebral or paranasal invasive fungal infection in a multinational study (53 proven AIFS) 2) 89 AIFS patients	1) Overall and AIFS-attributable mortality 2) Response to antifungal treatment	Symptoms included fever (67%), headache (17%), rhinorrhea (28%), and neurologic symptoms (17%)
Fernandez[23]	2018	3	Retrospective cohort	1) Patients >18 years old with proven AIFS 2) 19 AIFS patients; 1832 total patients	1) Overall survival 2) Efficacy of early intervention protocol	Disease progression: increased time for diagnosis was associated with increased mortality.
Raizada[8]	2018	3	Retrospective cohort	Patients with AIFS and DM ($n = 22$)	1) Survival 2) Radiographic response to treatment	Symptoms included facial pain/swelling (71.4%) loss of vision (68.2%), periorbital swelling/proptosis (63.6%)
Wandell[5]	2018	3	Retrospective cohort	AIFS patients >18 years old ($n = 114$)	1) Overall survival 2) Immunostimulating therapy	Symptoms included pain (65%), swelling (52%), congestion (43%), fever (42%), erythema (33%), necrosis (26%), numbness (18%), visual changes (18%), headache (18%), pupillary abnormalities (17%), drainage (17%), proptosis (13%), facial weakness (8%), and EOM weakness (7%).

(Continues)

TABLE 1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Roxbury[6]	2017	3	Retrospective cohort	Patients with AIFS ($n = 52$)	1) Short-term survival 2) Complete surgical resection	Symptoms included headache (53%), fever (46%), facial pain (36%), nasal congestion (32%), orbital pain (23%), rhinorrhea (21%), and visual change (19%)
Cohn[14]	2016	3	Retrospective cohort	1) Pediatric patients in treatment for hematologic malignancy; subset with AIFS 2) 13 AIFS patients	1) Mortality 2) Efficacy of an early intervention protocol 3) Symptoms	Symptoms before screening protocol were rhinorrhea, congestion, facial pain, and facial numbness; symptoms assessment after screening protocol showed that 62% of patients had no documented sinonasal symptoms or findings.
DelGaudio[24]	2009	3	Non-concurrent cohort	Patients diagnosed with AIFS ($n = 28$)	1) Involved subsites 2) Mortality 3) Morbidity	Fewer sites of involvement at diagnosis, fewer surgeries, and less long-term morbidity with early diagnosis
Ingley[25]	2008	3	Retrospective cohort	Patients with AIFS, single institution ($n = 48$)	1) Organism 2) Symptoms 3) Mortality	proptosis, periorbital edema, opthalmoplegia, cranial nerve deficits more common in Mucor than Aspergillus
Choi[26]	1995	3	Retrospective cohort	Pediatric bone marrow transplant patients, a subset developed AIFS (3 AIFS patients/80 patients)	1) Incidence of AIFS 2) Mortality	Presenting symptoms: nasal congestion, eyelid edema, headache
Gardner[27]	2021	4	Retrospective cohort	1) AIFS patients treated with surgery, at least 3 months follow-up ($n = 21$)	1) Survival	AIFS-specific mortality 28.6% at 2 weeks
Gur[28]	2021	4	Retrospective cohort	24 AIFS patients	1) Clinical data 2) Outcomes	Symptoms: Fever (41.6%), facial pain (37.5%), total visual loss and ophthalmoplegia (37.5%), nasal obstruction (29.1%), diplopia and partial ophthalmoplegia without visual loss (16.6%), hard palate wound (12.5%)
Sebastian[29]	2021	4	Case series	Patients with COVID-19 diagnosed with AIFS ($n = 3$)	1) Clinical parameters 2) Outcomes	Symptoms: mucosal necrosis (100%), facial swelling (67%), and proptosis (67%),
Coutel[30]	2021	4	Case series	3 patients with orbital spread of AIFS	1) Survival 2) Ophthalmologic outcomes	Vision loss with opthalmoplegia (66%) and abducens palsy (33%)
Wei[31]	2021	4	Case series	11 of 98 patients with AIFS without antifungal treatment in the 4 weeks before surgery	1) (1,3)-β-D-glucan and galactomannan levels	Symptoms: pain (90.1%), local swelling (45.5%), vision decline (45.5%), nasal congestion/runny nose (45.5%), proptosis (27.3%), diplopia (18.1%), ptosis (9.1%), facial numbness (9.1%), and fever (9.1%)

(Continues)

TABLE 1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Fadda[32]	2021	4	Case series	1) 17 patients with acute or chronic invasive fungal sinusitis 2) 4 of 17 AIFS	1) Presenting signs/symptoms 2) Survival 3) Disease relapse	Diplopia in 50%, abducens palsy in 50%, headache in 50%, and trigeminal neuralgia in 25%.
Zhang[16]	2020	4	Case series with low-quality systematic review	1) 4 patients with sphenoid AIFS 2) 68 patients in SR with cavernous sinus AIFS	1) Mortality and morbidity 2) Vision outcomes	Headache, vision impairment, and ophthalmoplegia in >50% of sphenoid sinus AIFS cases.
Hua[17]	2019	4	Case series	Single institution, 30 AIFS patients	1) Comorbidities 2) Fungal pathogen 3) Outcomes	Mortality was 54%. Symptoms: fever (64%), vision loss (36%), extraocular movement deficit (36%), ptosis (27%), and altered consciousness (27%).
Shanbag[33]	2019	4	Case series	14 patients presenting with AIFS	1) Diagnosis 2) Medicosurgical treatment	Symptoms: headache (25%), facial palsy (25%), palate lesion (25%), orbital/preseptal cellulitis (25%). Average of 9 days of symptoms prior to admission.
Cho[34]	2018	4	Case series	Patients with orbital apex lesions; 9 AIFS	1) Clinical features 2) Mortality	All AIFS patients had headache and orbital pain.
Vaughan[35]	2018	4	Case series	Rhino-orbital-cerebral mucormycosis from 1994 to 2015 (175 patients; low-quality meta-analysis of case reports/series)	1) Overall survival 2) Interval to medical and surgical treatment	Symptoms: periorbital/facial swelling (27%), fever (26%), decreased vision (20%), ptosis (18%), opthalmoplegia (15%), periorbital pain (14%), proptosis (11%), headache (5%), palate necrosis (5%), nasal ulceration (3%), and facial pain (3%)
Green[15]	2016	4	Case series	14 immunocompromised children with AIFS	Survival	Mortality was 14.3%, Symptoms of fever (93%), facial pain (64%) and nonspecific sinus symptoms (58%), rhinorrhea (42%), vision changes (29%), and facial or palate numbness (8%).
Ergun[36]	2016	4	Case series	AIFS patients ($n = 19$)	1) Symptoms 2) Underlying diseases 3) Causative fungus	Symptoms: headache/facial pain (47%), nasal crusting (26%), facial swelling (15%), palate lesion (15%), ocular symptoms (15%)
Bakhshaee[37]	2016	4	Case series	AIFS patients ($n = 18$)	1) Clinical features 2) Outcomes	Symptoms: headache and facial pain (77.8 %), facial paresthesia (55.6 %) and ophthalmoplegia (33.3 %)
Payne[38]	2016	4	Case series	AIFS patients ($n = 41$)	1) Clinical characteristics 2) Outcomes	fever (76%), pain (51%), nasal obstruction (45%), headache (30%), facial anesthesia (14.6%), loss of visual acuity/gaze palsy/ diplopia (26%)
Abdollahi[26]	2016	4	Case series	AIFS patients ($n = 15$)	1) Demographic and clinical data 2) Treatment 3) Outcomes	Symptoms: Periorbital swelling, ocular pain, ocular ptosis and proptosis, and loss of vision (86.7%), facial pain, swelling, and dysesthesia (80%), Nasal discharge, crust, turbinate necrosis (60%), headache (53%), fever (20%)

(Continues)

TABLE 1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Davoudi[7]	2015	4	Retrospective cohort	1) Hematologic malignancy patients who developed AIFS at single center 2) 44 AIFS patients	1) Clinical parameters 2) Survival	Symptoms: facial pain (54.6%), fever (45.5%), headache (45.5%), facial swelling (40.9%), nasal congestion (38.6%), sinus tenderness (31.8%), mucosal eschar (54.5%) nasal discharge (36.4%), facial erythema (22.7%), epistaxis (15.9%), facial numbness (13.6%), diplopia (13.6%), and blurred vision (11.4%).
Cho[39]	2015	4	Case series	Single institution, patients treated for AIFS between 1997 and 2013 ($n = 45$)	Disease-specific survival	78% disease specific survival; headache (42%), cranial nerve palsy (36%), visual loss (29%), and orbital pain (27%).
Lee[40]	2014	4	Case series	Patients with sphenoid AIFS ($n = 12$)	1) Mortality 2) Involvement of extra-sinus sites	Mortality was 100%. Presenting symptoms: visual disturbance (100%) and headache (50%).
Monroe[41]	2013	4	Case series	Single institution, surgically treated AIFS patients ($n = 29$)	Disease-specific survival	Symptom onset to diagnosis (7.6 ± 11 days); at onset: visual disturbances (24%), CNS symptoms (17%), and cranial neuropathy 24%.
Arora[42]	2011	4	Case series	Patients with rhino-orbital AIFS ($n = 5$)	1) Clinical presentation 2) Radiologic features 3) Visual and survival outcome	Proptosis (80%), unilateral blindness (60%), and ophthalmoplegia (60%).
Takahashi[43]	2011	4	Case series	AIFS patients ($n = 4$)	1) Mortality 2) Comorbidities	Headache was observed in all patients, and cranial nerve dysfunction (visual disturbance, cheek paresthesia) in 3 of 4.
Suslu[44]	2009	4	Case series	AIFS patients ($n = 19$)	1) Clinical features 2) Outcomes	Symptoms: nasal obstruction (94.7%), fever (73.7%), facial pain (68.4%), headache (42.1%), facial swelling (26.3%), black eschar (89.5%), and mucosal ulceration (21%).
Bhansali[45]	2005	4	Case series	Diabetic patients with AIFS ($n = 35$)	1) Clinical and demographic data 2) Outcomes	Signs/symptoms: proptosis (100%), ptosis (100%), ophthalmoplegia (85%), vision loss (85%), facial swelling (67%), nasal discharge (67%), altered mental status (33%), and palate perforation (16%).
Anselmo-Lima[46]	2004	4	Case series	Patients with AIFS ($n = 11$)	1) Clinical features 2) Outcomes	Persistent fever, nasal obstruction, headache, and purulent rhinorrhea; signs: nasal crusting (27%), septal perforation (9%).

(Continues)

TABLE 1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Sohail[47]	2001	4	Case series	AIFS patients ($n = 9$)	1) Presentation/symptoms 2) Treatment 3) Mortality	Symptoms: fever (100%), nasal obstruction (100%), headache (100%), facial induration (100%), proptosis (100%), facial swelling (100%), facial paralysis (44%), and nasal discharge (44%)
Kennedy[48]	1997	4	Case series	1692 bone marrow transplant patients, 29 with AIFS	Effect of early diagnosis protocol	Symptoms: fever (88%), facial pain (35%), congestion (23%); 64% diagnosed within 2 days of symptom onset.
Iwen[49]	1997	4	Case series	1) 17 patients with AIFS 2) 15 with hematologic malignancy; 2 with hepatic failure	1) Symptoms 2) Time to diagnosis 3) Survival	Most common symptoms include fever (100%), periorbital swelling (41%), nasal congestion (35%), and 47% survival.
Al-Bhlal[50]	1996	4	Case series	Fungal sinusitis, a subset was AIFS ($n = 9$)	1) Clinical features 2) Outcomes	Symptoms ionclude fever (56%) and facial pain (44%).
Yohai[51]	1994	4	Case series	Synthesis of case reports/series from literature from 1970 to 1994 ($n = 194$)	1) Clinical parameters 2) Outcomes	Symptoms include fever (44%), nasal ulceration/necrosis (38%), facial swelling (34%), decreased vision (30%), ophthalmoplegia (29%), headache (25%), facial pain (22%), altered mental status (22%), corneal anesthesia (17%), proptosis (16%), palatal necrosis (14%), and facial palsy (11%).
Drakos[52]	1993	4	Case series	11 of 423 bone marrow transplant patients who developed AIFS	1) Symptoms 2) Survival 3) Comorbidities	Fever (100%), orbital swelling (63%), facial pain (54%), and nasal congestion (36%).
Talbot[53]	1991	4	Case series	Patients with acute leukemia who developed AIFS ($n = 14$)	1) Clinical features 2) Outcomes	Symptoms: fever (100%), headache (50%), epistaxis (50%), cough (64%), mucosal crusting (57%), necrotic/dusky mucosa (21%), nasal ulcer (29%), and sinus tenderness (29%).
Blitzer[54]	1980	4	Case series	Patients diagnosed with paranasal mucormycosis ($n = 179$)	1) Clinical parameters 2) Outcomes	Symptoms include opthalmoplegia, facial swelling, proptosis, palatal ulcer, facial parasthesia, facial nerve weakness, and coma.

No articles were identified that described sensitivity, specificity, or predictive value of AIFS symptoms. One retrospective cohort study of high-risk patients with fever of unknown origin found that, although only those with AIFS exhibited decreased visual acuity, no symptom was significantly associated with AIFS diagnosis.[19] Payne et al.[38] described sensitivity and specificity of endoscopic signs for AIFS in immunocompromised patients, such as middle turbinate mucosal abnormalities (sensitivity, 54%; specificity, 88%), middle turbinate necrosis (37%, 97%), and septal mucosal necrosis (29%, 97%). Additional comparative studies such as prospective cohort studies would be useful to refine our knowledge of symptoms as well as determine whether specific signs and symptoms are predictive for early diagnosis of patients with AIFS among high-risk populations.

Aggregate Grade of Evidence: B (Level 2: 2 studies; Level 3: 13 studies; Level 4: 33 studies)

3.2 | Timing and acuity of presentation

There is evidence to suggest that time since symptom onset, which is related to extent of disease,[24] also influences symptoms present at diagnosis. Although the time course for AIFS has been defined as duration of symptoms progressing over less than 4 weeks,[59] few studies have described the specific time course of the disease in detail. Those not reporting this information typically utilized heterogeneous time intervals, such as days from neutropenia or bone marrow transplant until diagnosis or days from symptom onset to diagnosis or admission.[14,23,33,41,48,50] When timing of disease progression was reported, the disease course occurred over days to weeks, with a large fraction of disease-related mortalities occurring within the first 4 weeks of symptoms.[27,49,51,54]

Aggregate Grade of Evidence: C (Level 3: 3 studies; Level 4: 8 studies)

4 | LABORATORY AND MICROBIOLOGY DIAGNOSTICS

4.1 | Fungal identification

4.1.1 | Fungal culture and antifungal sensitivity

Tissue fungal culture is an important component of AIFS diagnosis and treatment.[7,17,28,31,33,60,61] Intraoperatively collected tissue or aspirates, not swabs, maximize yield.[62] Most estimates of culture sensitivity have ranged from 51.6% to 67%, with outlier estimates ranging from 36% to 90%.[7,57,60,61,63–65] When reported, estimated specificity ranged from 40% to 85.7% (95% confidence interval [CI], 57.2% to 98.2%).[60,63] Organism identification reduces invasive fungal infection mortality by guiding empiric antifungal choice, and phenotypic sensitivity testing helps tailor therapy.[56,64,66,67] Increased AIFS mortality has been reported when fungi cannot be cultured.[57,68]

Organism-specific prognostic data are conflicting. Some report poor prognostic associations for *Aspergillus* spp[7] or so-called "atypical" (non-*Aspergillus* spp/non-mucormycete) molds,[5] although the latter has not been consistently reproduced.[56] Others have identified[57] or suggested poorer outcomes with mucormycosis.[27,68] Culture sensitivity may be decreased for mucormycetes and non-*Aspergillus* spp/non-mucormycete molds.[60,61,64] Turnaround time of at least 5 days is a limitation of culture.[60,63] Table 2 summarizes evidence surrounding use of fungal culture and sensitivities for AIFS diagnosis.

Aggregate Grade of Evidence	**C (Level 2: 2 studies; Level 3: 3 studies; Level 4: 9 studies)**
Benefit	Fungal cultures are important for speciation as different organisms have different antimicrobial susceptibility profiles and affect prognosis. When combined with histopathology, the sensitivity and rate of correct diagnosis is increased compared with either alone.
Harm	Tissue culture requires either a bedside procedure or general anesthesia in the operating room to acquire a sample, each carrying its own morbidity. Cultures can take up to 7 days to result and can yield no growth.
Cost	Delayed diagnosis.
Benefit–Harm Assessment	When used to supplement histopathology, fungal species identification carries a benefit for diagnosis and management of AIFS. Tissue samples for culture can be obtained during the procedure to obtain samples for histopathology with very little additional morbidity.
Value Judgment	Culture is important for fungal species identification and to supplement histopathology for improved diagnostic accuracy.
Policy Level	Recommendation: Recommend obtaining tissue cultures whenever possible.
Intervention	Obtain tissue samples for culture when working up a patient for AIFS.

TABLE 2 Fungal culture and antifungal sensitivity.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lieberman[60]	2021	2	Retrospective review	52 patients with suspected AIFS and available culture and PCR results	1) Diagnosis 2) Fungal identification	Culture complements other diagnostic tools, but it has modest sensitivity and longer turnaround time.
Raiesi[64]	2021	3	Prospective cross-sectional	Confirmed AIFS ($n = 33$)	1) Diagnosis 2) Fungal identification	Cultures are useful, but less sensitive in the identification of rare fungi.
Wei[31]	2020	3	Retrospective cohort	Patients with space-occupying lesions in the nasal cavity and sinuses where initial diagnosis did not exclude AIFS (11 of 98 with AIFS)	Diagnosis	While fungal culture is useful in species identification, it should not be used as the sole method for identification.
Badiee[61]	2016	3	Prospective observational cohort	31 patients with suspected AIFS, 18 with confirmed AIFS	Diagnosis	Tissue culture aids in the identification of fungal elements and species.
Gur[28]	2021	4	Retrospective review	24 patients diagnosed with mucor	1) Diagnosis 2) Disease-specific mortality	Tissue culture alone is not sufficient for diagnosis of AIFS but is supplemental to histopathology.
Hirabayashi[57]	2019	4	Retrospective review individual cohort	55 patients with biopsy proven AIFS	1) Visual acuity 2) Outcomes 3) Orbital exenteration 4) Mortality	Fungal culture and species identification are important for prognosis.
Hua[17]	2019	4	Retrospective review	22 patients with AIFS	1) Diagnosis 2) Survival	Fungal culture should be performed in AIFS.
Shanbag[33]	2019	4	Case series	8 patients with proven AIFS	Survival	Fungal culture is required in the workup of AIFS and should supplement histopathology.
Silveira[63]	2019	4	Retrospective review–cohort	43 patients with proven AIFS	Survival	Culture is helpful for fungal identification but has its limitations, including lack of fungal growth and extended time to results.
Vengerovich[56]	2019	4	Case series	34 patients with biopsy-proven AIFS	Outcomes	Culture may help direct selection of antifungal therapy as it can identify AIFS that is polyfungal or due to atypical fungi.
Davoudi[7]	2015	4	Retrospective review	40 proven and 4 probable AIFS patients with hematologic malignancies	Survival at 6 and 12 weeks	Fungal culture in addition to histopathology are highly effective for diagnosing AIFS. Fungal identification may have survival implications.
Montone[65]	2012	4	Retrospective review	AIFS patients ($n = 44$)	Culture results diagnosis	Culture can be used to identify fungal pathogens and to complement histopathology.
Chen[68]	2011	4	Retrospective case–control	Proven AIFS ($n = 25$), probable AIFS ($n = 5$), possible AIFS ($n = 16$), controls were patients with hematologic malignancy and noninvasive sinusitis	Survival	Fungal identification is important for prognosis.

4.1.2 | Direct microscopic examination of tissue specimens

Direct microscopy of specimens with potassium hydroxide (typically fluorescence microscopy) is frequently a component of fungal cultures. It provides rapid information about the presence of fungi and is analogous to intraoperative examination (see section VIII: Pathology). The estimated sensitivity ranges from 28.6% to 60%, and specificity ranges from 33.3% to 100%.[7,33,60] Direct examination can detect fungus even in cases when culture and/or PCR are negative. A major drawback is the inability to determine pathogen identity, because molds in tissue lack species-identifying characteristics.[69] Table 3 summarizes evidence surrounding use of direct microscopic examination of tissue for AIFS diagnosis.

Collectively, fungal culture, direct examination, and antifungal susceptibility testing are recommended in cases of AIFS and can detect cases missed by other assays.[60] A single sample is usually sufficient for multiple assays, including culture and PCR.

Aggregate Grade of Evidence	C (Level 2: 1 study; Level 3: 1 study; Level 4: 2 studies)
Benefit	Microscopic direct tissue examination can aid in the diagnosis of AIFS.
Harm	Sampling error can lead to a false negative diagnosis. Potassium hydroxide, Grocott–Gomori methanamine silver, and hematoxylin–eosin staining may not identify fungal elements and cannot provide fungal species information.
Cost	If fungal elements are not identified, there may be a delay in AIFS diagnosis and treatment.
Benefit–Harm Assessment	Direct examination of tissue for fungal elements can provide a rapid diagnosis of AIFS if fungal elements are seen. False-negative results are possible, but this can be worked around using direct examination as a complement to culture, PCR, and histopathology.
Value Judgment	Direct examination can be used to promptly identify fungal organisms in tissue during the workup of AIFS.
Policy Level	Recommendation: Recommend using direct examination of tissue during the workup of AIFS.
Intervention	During the workup of suspected AIFS, direct examination of tissue should be performed in conjunction with cultures, PCR, and histopathology.

TABLE 3 Direct microscopic examination of tissue specimens.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lieberman[60]	2021	2	Retrospective review	52 patients with suspected AIFS and available culture and PCR results	1) Diagnosis 2) Fungal identification	Direct microscopic exam has rapid turnaround, and complements PCR and culture, but has lower sensitivity and may not provide organism identification.
Badiee[61]	2016	3	Prospective observational cohort	31 patients with suspected AIFS, 18 with confirmed AIFS	Diagnosis	Direct microscopic exam using histopathology or KOH may be more sensitive than culture in diagnosing AIFS.
Shanbang[33]	2019	4	Case series	Eight patients with proven AIFS	Survival	Direct examination (KOH) is a screening test with sensitivity (60%) and specificity (33.33%).
Davoudi[7]	2015	4	Retrospective review	40 proven and 4 probable AIFS patients with hematologic malignancies	Survival at 6 and 12 weeks	Tissue staining with GMS or H&E may be more sensitive than fungal smears in diagnosing AIFS.

AIFS, acute invasive fungal sinusitis; GMS, Gomori methenamine silver; H&E, hematoxylin and eosin; KOH, potassium hydroxide; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

4.1.3 | PCR

Broad-range PCR is an efficient diagnostic tool for invasive fungal infections and for identifying the culprit fungal species. The few studies specific to AIFS are consistent with data across invasive fungal infection literature supporting the use of molecular diagnostics as a complement to traditional methods.[70–74]

A large retrospective review examining utility of broad-range PCR in the diagnosis of AIFS found performing PCR on resected tissue alone had a sensitivity of 85.0% (95% CI, 70.1% to 94.3%), better than with tissue culture alone (67.5%; 95% CI, 50.9% to 81.4%), whereas the specificities of both methods were 85.7% (95% CI, 57.2% to 98.2%). Together, PCR-positive culture had a diagnostic sensitivity of 90.0% (95% CI, 76.3% to 97.2%) and specificity of 78.5% (95% CI, 49.2% to 95.3%).[60] PCR provided preliminary and final results with fungal identification to the species level more expeditiously than culture.[60] Raiesi et al. reported 100% of their 33 AIFS patients had identification of fungal species with broad-range PCR compared with 17 of 33 positive cultures. Using PCR as a complement to culture may increase the ability to detect polyfungal infections.[60,74] Broad-range fungal PCR performed on tissue is recommended as an adjunct to mycologic culture as combining these assays increases sensitivity and decreases turnaround time.

Serum PCR has been used in the workup of IFIs and may adequately rule out invasive aspergillosis in high-risk groups.[72] Of 18 patients with AIFS proven on histopathology, 6 (5 *A flavus* on culture, 1 no growth) had positive serum PCR results.[61] As data and clinical assay availability of PCR and serum-based molecular tests are limited, we cannot make recommendations regarding either for the diagnosis of AIFS. Table 4 summarizes evidence surrounding use of PCR for AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 2: 1 study; Level 3: 3 studies)
Benefit	Preliminary and final results are available more quickly than culture. There is an increased ability to identify fungal species, including rare species that are difficult to identify morphologically.
Harm	Lack of diagnosis if the fungus has not been sampled adequately.
Cost	Serum PCR requires blood draws and tissue PCR requires tissue samples. Adding a further blood draw to a hospitalized patient may cause increased pain/morbidity, but it can be added to the complement of blood samples already being collected. Collecting tissue samples requires either a bedside procedure or general anesthesia in the operating room, both of which carry risk and morbidity.
Benefit–Harm Assessment	Tissue is required to histopathologically diagnose AIFS. Additional samples for PCR would add little morbidity or risk and would add the benefit of more expedient fungal species identification.
Value Judgment	PCR is complementary to culture.
Policy Level	No recommendation: Insufficient data is available to make recommendations on serum/plasma-based molecular assays. Recommendation: Recommend PCR testing on tissue to identify fungal organisms when evaluating and treating a patient for AIFS as there is significant additional benefit with little to no added morbidity.
Intervention	When obtaining blood samples during patient workup and tissue samples for histopathologic diagnosis of AIFS, samples should be obtained and sent for PCR testing for fungal elements.

4.2 | Serum biomarkers

4.2.1 | β-D-glucan

Serum analysis for the fungal cell wall constituent (1,3)-β-D-glucan (BDG) has been used to detect IFIs, although data are conflicting on diagnostic accuracy.[75] Several antibiotics, bacteremia, and malignancy can cause false-positive results and BDG is not specific to a fungal species.[31,75,76] Heterogeneous cutoffs (>151.5, >59, and >30 pg/mL) have been used to examine diagnostic accuracy and prognosis in a limited number of patients, often too small to calculate meaningful statistics.[27,31,43] Although these tests may not be readily available at all hospital systems, they are routinely used in the field of infectious diseases and play a role in the diagnosis of AIFS. As the data are limited, further study is needed to

TABLE 4 PCR.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lieberman[60]	2021	2	Retrospective review	52 patients with suspected AIFS and available culture and PCR results	1) Diagnosis 2) Fungal identification	PCR complements culture in the management of AIFS. Preliminary results are available faster with more specific organism identification.
Raiesi[64]	2021	3	Prospective cross-sectional	108 patients with confirmed sinonasal fungal infections, 33 with AIFS	1) Diagnosis 2) Fungal identification	PCR allows for unambiguous identification of most fungi and for the identification of rare species that may be difficult to classify using culture.
Badiee[61]	2016	3	Prospective observational cohort	31 patients with suspected AIFS, 18 of those with AIFS	Diagnosis	Using specific PCR targeting several species of fungi, screening high-risk patients with serum PCRs may aid in early diagnosis.
Zhao[74]	2011	3	Assay development	98 validated isolates tested against 28 FFPE and 13 fresh specimens	Diagnosis	PCR/reverse line blot may be more sensitive than PCR alone for fungal identification.

AIFS, acute invasive fungal sinusitis; FFPE, formalin fixed paraffin embedded; PCR, polymerase chain reaction; RLB, reverse line blot.

TABLE 5 Beta-D-glucan.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wei[31]	2020	3	Retrospective cohort	Patients with space-occupying lesions in the nasal cavity and sinuses where initial diagnosis did not exclude AIFS (11 of 98 with AIFS)	Diagnosis	Serum BDG independently or in conjunction with serum GM may aid in the diagnosis of AIFS.
Gardner[27]	2021	4	Retrospective review	21 patients with biopsy-proven AIFS	Survival at 3 months	Serum BDG may aid in diagnosis of AIFS.
Takahashi[43]	2011	4	Case series	4 patients with AIFS involving the cavernous sinus and orbit	Resolution of disease death	Serum BDG may aid in the diagnosis of AIFS.

AIFS, acute invasive fungal sinusitis; BDG, beta-D-glucan; GM, galactomannan.

determine BDG utility in the diagnosis of AIFS. Table 5 summarizes evidence surrounding use of BDG for AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 2 studies)
Benefit	Serum BDG may aid in the diagnosis of AIFS.
Harm	Blood samples are required. There is a non-negligible rate of both false positives and false negatives that needs to be taken into consideration.
Cost	Missed diagnoses and false-positive results are a risk.

Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 2 studies)
Benefit–Harm Assessment	Serum BDG can add additional information during the workup of AIFS. However, its results are difficult to interpret individually due to rates of false negatives and false positives.
Value Judgment	Consider using serum BDG in addition to alternative methods of diagnosing AIFS.
Policy Level	No recommendation: Further studies are necessary to establish the accuracy of serum BDG and its use in the diagnosis of AIFS
Intervention	Consider obtaining serum BDG during the workup of AIFS.

4.2.2 | Galactomannan

Like BDG, galactomannan (GM) is a fungal cell wall component and established serum biomarker of invasive fungal infections that can aid in, but is not sufficient for, diagnosis of AIFS.[7,19,27,68,77–79] Although frequently treated as a biomarker for *Aspergillus spp* IFIs, GM cross-reacts with a broad array of organisms including *Fusarium* and mucormycetes.[7,78] Reported cross-reactivity with β-lactam antibiotics is disputed.[23,76–78] A recent meta-analysis estimated an area under the curve (AUC) of 0.65 for diagnosing AIFS with *Aspergillus* spp at a cutoff GM index of 0.5.[80] Sensitivity was frequently estimated at 40% to 45%, with outliers of 15.7% and 65%.[7,19,27,61,68] Multiple studies estimated GM specificity of ≥95%; one conflicting report estimated 60% specificity.[19,68,77,79]

These data indicate GM can supplement diagnosis of AIFS in combination with microscopy/histopathology and culture/PCR. However, the assay does not identify the pathogen and may be susceptible to false positives and false negatives. Table 6 summarizes evidence surrounding use of galactomannan for AIFS diagnosis.

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 3 studies; Level 4: 5 studies)**
Benefit	Serum GM can be used to aid in the diagnosis of AIFS.
Harm	Blood samples are required. It is more associated with invasive *Aspergillus* infections, which is one of many fungi that may cause AIFS. There is a non-negligible rate of false positivity that must be taken into consideration.
Cost	Missed diagnoses and false-positive results are a risk.
Benefit–Harm Assessment	When used as a part of the workup of AIFS, serum GM levels can be useful to raise suspicion and aid in diagnosis. Any harm from missed diagnoses/false positives can be tempered by using serum GM as a supplement and not as the only method.
Value Judgment	Use serum GM in addition to alternative methods to diagnose AIFS.
Policy Level	Option: Obtaining serum GM is an option in the workup of AIFS.
Intervention	Serum GM can be obtained as a supplement to other, more well-established means of diagnosis but should not be utilized as a stand-alone diagnostic test for AIFS due to significant limitations.

4.3 | Prognostic biomarkers

4.3.1 | Leukocyte counts

Neutropenia is defined as absolute neutrophil count (ANC) <1000 $10^3/\mu$L, <500 $10^3/\mu$L, <100 $10^3/\mu$L, or equal to 0 $10^3/\mu$L, depending on the study. Nonetheless, the consensus is to approach all neutropenic patients with high suspicion. Neutropenia or prolonged neutropenia may be associated with increased mortality, and ANC recovery may be associated with improved survival.[4,5,7,15,27,28,38,39,44,57,63,68,82–84] Notably, ANC >1000 does not preclude AIFS.[17] Data are conflicting regarding ANC's prognostic utility, and no accepted level or range has been surely associated with diagnosis or prognosis. Absolute lymphocyte count (ALC) may be associated with all-cause mortality when <200.[7] More studies are needed to elucidate ANC and ALC as diagnostic and prognostic variables for AIFS. Table 7 summarizes evidence surrounding use of leukocyte count for AIFS diagnosis.

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 2 studies; Level 4: 12 studies)**
Benefit	ANC provides a great deal of information on a patient's level of immunosuppression. As neutropenia may convey an increased risk of AIFS, obtaining this lab may increase the level of suspicion for AIFS. ANC trends in neutropenic patients may provide useful prognostic information. Obtaining an ANC requires little increased morbidity.
Harm	ANC trends may not apply to causes of immunosuppression other than hematologic malignancy. Some data are conflicting on the prognostic utility of ANC.
Cost	Relying on ANC to gauge level of suspicion or provide a prognosis could lead to missed AIFS diagnoses, sinus surgery for a tissue sample in a patient who otherwise has low suspicion for AIFS, and commitment to an incorrect prognosis.
Benefit–Harm Assessment	Using ANC and its trends as a complement to other indicators of suspicion and diagnostic modalities and considering it as a part of the whole picture when assessing prognosis is beneficial to planning the workup and treatment of patients with proven or probable AIFS. The benefit of raising suspicion and obtaining tissue for diagnosis/rule-out of AIFS (a disease that can be rapidly fatal if diagnosis is delayed or missed) may outweigh the risk and morbidity of a sinus procedure.

TABLE 6 Galactomannan.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Chang[77]	2021	2	Meta analysis[a]	118 total patients, 62 with confirmed *Aspergillus* AIFS	*Aspergillus* AIFS and serum galactomannan	Serum GM can be used in addition to other methods to diagnose AIFS.
Lagos[19]	2021	3	Prospective cohort	50 patients with suspected AIFS	Diagnosis of AIFS	GM is a useful supplement in the diagnosis of AIFS, but can yield false-positive results.
Wei[31]	2020	3	Retrospective cohort study	Patients with space-occupying lesions in the nasal cavity and sinuses where initial diagnosis did not exclude AIFS (11 of 98 with AIFS)	Diagnosis	Serum GM independently or in conjunction with serum BDG may aid in the diagnosis of AIFS.
Badiee[61]	2016	3	Prospective observational cohort	31 consecutive high-risk patients with clinical signs and symptoms of IFS	Diagnosis	Serum GM can be used to aid in the diagnosis of AIFS. Consider use when tissue sampling is not possible.
Gardner[27]	2021	4	Retrospective review	21 patients with biopsy-proven AIFS	Survival at 3 months	Serum GM may aid in diagnosis of AIFS.
Melancon[79]	2019	4	Retrospective review	38 patients with path evaluated for AIFS and serum GM results	Diagnosis	An elevated serum GM with high suspicion of AIFS should undergo biopsy. Serum GM should not be used to screen for AIFS.
Cho[78]	2016	4	Retrospective case–control, control group data was collected prospectively	28 consecutive patients with AIFS vs. patients with fungal balls	GM level survival	Serum GM should be measured in the workup of patients at high risk of AIFS. Persistently elevated serum GM may be a predictor of mortality.
Davoudi[7]	2015	4	Retrospective review	40 proven and 4 probable AIFS patients with hematologic malignancies over 10 years	Survival at 6 and 12 weeks	Serum GM level is indicative of *Aspergillus* AIFS, but should not be used as the sole method of diagnosis as there is a risk of false positivity.
Chen[81]	2011	4	Retrospective case control	Proven AIFS ($n = 25$), probable AIFS ($n = 5$), and possible AIFS ($n = 16$); controls were patients with hematologic malignancy and noninvasive sinonasal malignancy and noninvasive sinusitis	Survival	Serum GM can be used to assist with diagnosis of AIFS.

GM, galactomannan.

[a]Downgraded due to inclusion of prospective and retrospective cohort studies only (no randomized controlled trials available).

TABLE 7 Leukocyte counts.

Study	Year	LOE	Study Design	Study groups	Clinical endpoint	Conclusion
Turner[4]	2013	2	Systematic review	807 patients from 52 AIFS studies	Prognostic factors (survival)	Neutropenia and prolonged neutropenia may be associated with increased risk of mortality.
Wandell[5]	2018	3	Multisite retrospective cohort study	Biopsy-proven AIFS from 3 academic institutions ($n = 114$)	1- and 3-month survival	Non-neutropenic patients with HM may be at risk for AIFS. Persistent neutropenia may be associated with decreased survival.
Chen[68]	2011	3	Retrospective case–control	Proven AIFS ($n = 25$), probable AIFS (n = 5), and possible AIFS ($n = 16$); controls were patients with hematologic malignancy and noninvasive sinusitis	Survival	Prolonged neutropenia may be associated with increased risk of AIFS and increased risk of mortality.
Gardner[27]	2021	4	Retrospective review	21 patients with biopsy-proven AIFS	Survival at 3 months	ANC = 0 mm^3 may not increase risk of mortality.
Gur[28]	2021	4	Retrospective review	24 patients diagnosed with mucor AIFS	Disease-specific mortality	Neutropenia may not have an association with mortality in AIFS when *Mucor* is the pathogen.
Parasher[82]	2019	4	Case–control, retrospective observational	Four patients with posttransplant lymphoproliferative disease of paranasal sinuses; 10 patients with AIFS after a transplant	Diagnosis	Neutropenia may be associated with AIFS.
Hirabayashi[57]	2019	4	Retrospective review	55 patients with biopsy-proven AIFS	1) Visual acuity 2) Outcomes 3) Exenteration 4) Mortality	Neutropenia may increase risk of mortality.

(Continues)

TABLE 7 (Continued)

Study	Year	LOE	Study Design	Study groups	Clinical endpoint	Conclusion
Silveira[63]	2019	4	Retrospective review	43 patients with suspected AIFS	Survival	Neutropenia may be associated with disease-specific mortality.
Payne[38]	2016	4	Retrospective review	131 patients who received otolaryngology consult to rule out AIFS	1) Diagnosis 2) Survival	Clinical suspicion for AIFS should be elevated in patients with severe neutropenia.
Green[15]	2016	4	Retrospective review	14 patients with AIFS with 6 months of follow-up	Disease specific survival	Recovery of ANC to normal levels may be associated with increased disease-specific survival.
Gode[84]	2016	4	Retrospective review	37 patients who underwent surgery for AIFS	1) Overall survival 2) Disease-free survival	Neutropenia may be associated with an increased rate of mortality.
Davoudi[7]	2015	4	Retrospective review	40 proven and 4 probable AIFS patients with hematologic malignancies	Survival at 6 and 12 weeks	Lymphopenia and severe neutropenia may be associated with increased mortality
Cho[39]	2015	4	Retrospective review	45 patients with AIFS	Overall survival	Severe neutropenia may be associated with an increased risk of mortality.
Suslu[44]	2008	4	Retrospective review	19 patients with diagnosed AIFS	Survival	Neutropenia may be associated with increased risk of disease-specific mortality.
Parikh[83]	2004	4	Retrospective review	43 patients with AIFS	1) Disease-specific mortality 2) Overall survival	Recovery of ANC to normal levels may be associated with increased disease specific survival.

AIFS, acute invasive fungal sinusitis; ANC, absolute neutrophil count; HM, hematologic malignancy.

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 2 studies; Level 4: 12 studies)**
Value Judgment	ANC levels should be obtained as part of the workup and monitoring of patients with probable or proven AIFS. This is particularly important in those with hematologic malignancies.
Policy Level	Recommendation: Recommend obtaining and trending ANC levels in patients with probable or proven AIFS.
Intervention	ANC levels should be used to complement additional diagnostic modalities for AIFS. ANC levels can be used to aid in the prognosis of patients with AIFS in conjunction with other modalities and clinical judgment, but more studies are needed to determine ANC-level cutoffs for prognosis.

4.3.2 | Serum glucose and hemoglobin A1C

A systematic review of 807 patients with AIFS demonstrated diabetes mellitus (DM) prevalence of 47.8%, including 23.1% who presented in diabetic ketoacidosis. These patients also presented with other risk factors, including 39% with a hematologic malignancy, 27.6% with corticosteroid treatment, 6.3% with solid-organ transplantation, 2.3% with human immunodeficiency virus/acquired immunodeficiency syndrome, and 1.2% with an autoimmune disease. However, prognostic analysis completed on 398 patients found that DM was a positive prognostic indicator in univariate and multivariate analyses ($p = 0.032$; odds ratio [OR], 0.641, 95% CI; 0.427 to 0.962 and $p = 0.003$; OR, 0.492; 95% CI, 0.308 to 0.788) as compared with other immunosuppressive diagnoses.[4] A review of 114 patients was concordant, reporting improved survival at 1 and 3 months in patients with DM and a higher hemoglobin A1C.[5] Improved AIFS survival in diabetic patients is hypothesized to reflect protection from the relative reversibility of their immune compromise, as tight blood glucose (BG) control may be associated with improved survival.[33] Table 8 summarizes evidence surrounding use of glycemic indices for AIFS diagnosis.

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 1 study; Level 4: 4 studies)**
Benefit	As elevated BG may be associated with increased risk of mortality, trending BG for tight control may improve disease-free survival.

TABLE 8 BG and glycemic indices.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Turner[4]	2013	2	Systematic review	807 patients from 52 AIFS studies	Prognostic factors (survival)	DM may be associated with an increased rate of survival.
Wandell[5]	2018	3	Multisite retrospective cohort study	Biopsy-proven AIFS from 3 academic institutions ($n = 114$)	1- and 3-month survival	DM may be associated with improved survival.
Davoudi[7]	2015	4	Retrospective review	40 proven and 4 probable AIFS patients with hematologic malignancies	Survival at 6 and 12 weeks	Elevated BG may be associated with mucor infection.
Gur[28]	2021	4	Retrospective review	24 patients diagnosed with *Mucor*	1) Diagnosis 2) Disease-specific mortality	Elevated BG may be associated with mortality in diabetic patients with *Mucor* AIFS.
Shanbag[33]	2019	4	Case series	8 patients with AIFS	Survival	Controlling BG may be associated with an increased rate of survival.
Cho[39]	2015	4	Retrospective review	45 patients with AIFS	Overall survival	DM may be associated with an increased risk of mortality.

AIFS, acute invasive fungal sinusitis; BG, blood glucose; DM, diabetes mellitus.

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 1 study; Level 4: 4 studies)**
Harm	Additional lab draws and/or needle sticks.
Cost	Tight BG control requires a multidisciplinary approach to close monitoring as well as additional lab draws and/or needle sticks and insulin.
Benefit–Harm Assessment	Elevated BG may be associated with increased mortality in diabetic patients with AIFS, a rapidly fatal disease. Controlling BG is critical not only for managing the patient's diabetes, but to increase the likelihood of AIFS remission and survival.
Value Judgment	Trending BG and maintaining strict BG control should be part of the workup and treatment plan for diabetic patients with AIFS.
Policy Level	Recommendation: Recommend trending and maintaining strict BG control in diabetic patients with AIFS.
Intervention	Trend and maintain strict BG control in diabetic patients with AIFS.

4.3.3 | C-reactive protein

C-reactive protein (CRP) has been analyzed as a prognostic factor, yet data are conflicting and more studies are needed.[5,28,39,84] As such, we cannot make a recommendation regarding CRP in patients with AIFS. Table 9 summarizes evidence surrounding use of CRP for AIFS diagnosis.

Aggregate Grade of Evidence: C (Level 3: 1 study; Level 4: 3 studies)

5 | ENDOSCOPY

Bedside nasal endoscopy is widely used as a diagnostic procedure during the initial work-up to evaluate the nasal cavity when there is clinical concern for AIFS. However, due to patient intolerance and inability to completely view the sinuses, there are obvious limitations in practice. Abnormalities suggestive of AIFS have included mucosal edema, discoloration (e.g., pallor or darkened tissue), ulceration, and lack of sensation. In general, select nasal endoscopy findings for AIFS are considered highly specific, but have a wide range in reported sensitivity, ranging from 49% to 75%.[7,19,38,58,63,85,86]

In the pediatric population, in which the decision for general anesthesia for operative biopsies and debridement may pose a higher threshold, the value of bedside endoscopy has also been investigated. Park et al. demonstrated that, in the pediatric population, bedside

TABLE 9 CRP.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wandell[5]	2018	3	Multisite retrospective cohort study	Biopsy-proven AIFS from 3 academic institutions ($n = 114$)	1- and 3-month survival	CRP may have no effect on survival.
Gur[28]	2021	4	Retrospective review	24 patients diagnosed with mucor	1) Diagnosis 2) Disease-specific mortality	CRP may have no impact on disease-specific mortality.
Cho[39]	2015	4	Retrospective review	45 patients with AIFS	Overall survival	Elevated CRP at diagnosis may be associated with an increased risk of mortality.
Gode[84]	2015	4	Retrospective review	37 patients who underwent surgery for AIFS	1) Overall survival 2) Disease-free survival	Elevated CRP may be associated with an increased risk of disease-specific mortality.

AIFS, acute invasive fungal sinusitis; CRP, C-reactive protein.

endoscopy did not correlate with ultimate diagnosis of AIFS, whereas operative endoscopic abnormalities were associated with the diagnosis of AIFS.[86] However, Mulvey et al. found diagnostic value in bedside endoscopy in the pediatric population.[58]

Although nasal endoscopy has been discussed as a diagnostic procedure in AIFS surveillance, routine surveillance nasal endoscopy has not been widely studied in the literature. Silveira et al. described repeat endoscopic exams every 24 to 48 hours after surgical debridement and found that 40% (14 of 35) of patients who had undergone endoscopic debridement required further operative debridement after new mucosal abnormalities were identified.[58]

Overall, the utility of nasal endoscopy appears to be high when mucosal lesions are present in the regions of the nasal cavity that can be tolerably and readily examined at the bedside. However, mucosal changes on endoscopic exam may indicate relatively late-stage disease. Further, limitations of nasal endoscopy include inability to visualize within the paranasal sinuses in nonoperated patients, and in those that have had AIFS surgery subsequent endoscopy (e.g., bedside) can be limited by crusting, packing, or debris. Given the low time and cost investment of nasal endoscopy as well as high reported specificity of mucosal lesions, nasal endoscopy is highly useful when mucosal abnormalities are seen. However, in its current utilization, nasal endoscopy lacks the sensitivity of an optimal screening tool. Table 10 summarizes evidence surrounding use of bedside endoscopy for AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 6 studies)
Benefit	Endoscopy affords efficient diagnosis when mucosal abnormalities are present without the need for general anesthesia.
Harm	Minimal harm to the patient, given that bedside assessment can be performed as part of the physical exam. As sensitivity is low, there is a risk of false-negative results, especially for undissected sinuses where deeper structures may be involved with infection, leading to delay in definitive treatment.
Cost	Direct costs include standard processing of endoscope hardware in facilities where endoscopic equipment and appropriately trained providers are available.
Benefit–Harm Assessment	Benefit of direct visualization of the nasal cavity and general ease of performance likely outweighs harm.
Value Judgments	Given the reported high specificity, mucosal abnormalities on endoscopic exam may help expedite diagnosis and treatment. However, a negative endoscopic exam in the setting of high clinical suspicion for invasive fungal disease warrants continued workup.
Policy Level	Recommendation: Recommend endoscopy for AIFS evaluation.
Intervention	Bedside endoscopic evaluation is a recommendation for AIFS work-up, given the overall low-risk profile and ease of execution. Specificity of this exam is high; however, sensitivity is low, and a normal endoscopy alone should not be used to rule out disease.

6 | BIOPSY

After initial endoscopic examination and imaging, biopsy is often the next consideration in the workup algorithm of AIFS. Bedside biopsy affords a relatively low cost and efficient means of tissue sampling. Diagnostic yield in suspected AIFS is highest when there are visible abnormalities on endoscopic exam. However, bedside biopsies in patients with coagulopathy, thrombocytopenia, and other medical comorbidities, as are often the case in AIFS, pose challenges. In addition, minimal tissue is comfortably obtained in an awake patient. In the absence of obvious AIFS findings, biopsy is subject to sampling bias, thus further limiting its diagnostic utility. In a review examining four retrospective studies, authors concluded that evidence in support of bedside biopsy to diagnose AIFS with high fidelity is lacking.[87]

Most studies have investigated frozen section analysis of bedside biopsies to assess for invasive fungal elements. The most common anatomic biopsy site described is the middle turbinate. Ghadali et al. and Gillespie et al. reported sensitivity of middle turbinate biopsy at 84% and 74%, respectively.[88,89] Silveira et al. investigated targeted bedside biopsies of mucosa with discoloration and reported 91% sensitivity, but a lower specificity was reported (73%) when compared with the aforementioned studies.[63]

Fine-needle aspiration biopsy (FNAB) is another tool that has been reported in the literature to aid in bedside workup of AIFS.[90,91] Fine-needle aspiration can be performed with CT guidance, endoscopic guidance, or percutaneously using anatomic landmarks. There were no reported complications of FNAB in the literature.

In summary, bedside biopsy can provide additional data to support the diagnosis of AIFS. However, the presence

TABLE 10 Bedside endoscopy.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Lagos[19]	2021	3	Cohort study	50 patients with suspected AIFS, 9 patients with confirmed AIFS	Diagnostic accuracy of bedside nasal endoscopy for detection of AIFS.	Healthy mucosa was statistically associated with non-AIFS diagnosis, but necrotic mucosae were only seen in 7 of 9 (77.8%) AIFS patients on endoscopic exam.
Yin[85]	2021	4	Retrospective review	283 suspected AIFS patients, 39 confirmed AIFS patients	Diagnostic accuracy of bedside nasal endoscopy for detection of AIFS	Nasal mucosa necrosis on endoscopy; sensitivity 49% and specificity 98%.
Silveira[63]	2019	4	Retrospective review	43 confirmed AIFS patients	Mortality by anatomical subsite on endoscopy	Thirty-one of 43 patients had pale or darkened middle or inferior turbinates, and 7 of 31 died. Twelve of 43 had a pale or darkened septum or lateral nasal wall, and 7 of 12 died.
Mulvey[58]	2017	4	Retrospective review	19 pediatric patients with suspected AIFS	Diagnostic accuracy of bedside nasal endoscopy for detection of AIFS	Bedside endoscopy with mucosal abnormalities: sensitivity 75% and specificity 100%.
Payne[38]	2016	4	Retrospective review	131 patients with suspected AIFS, 41 with confirmed AIFS	Diagnostic accuracy of bedside nasal endoscopy for detection of AIFS	Middle turbinate abnormalities: 54% sensitivity and specificity 88%. Septum abnormalities: sensitivity 29% and specificity 97%. Middle turbinate necrosis: sensitivity 37% and specificity 97%.
Davoudi[7]	2015	4	Retrospective review	44 AIFS patients	Diagnostic accuracy of bedside nasal endoscopy for detection of AIFS	Bedside endoscopic with black eschar or necrosis; sensitivity 55%.
Park[86]	2005	4	Retrospective review	9 confirmed AIFS patients	Diagnostic accuracy of bedside versus operative endoscopy	Nasal mucosa edema, ulceration, or necrosis found; sensitivity 50% and specificity 90%.

TABLE 11 Bedside biopsy.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Silveira[63]	2019	4	Retrospective review	43 confirmed AIFS patients	Diagnosis of AIFS on bedside biopsy by frozen section	Sensitivity of frozen section biopsy 90.6%; specificity 72.7%; PPV 90.6%; NPV 72.7%, and accuracy 86.0% ($p < 0.0001$).
Singhal[90]	2013	4	Retrospective review	9 at-risk AIFS patients of which 8 ultimately diagnosed with AIFS	Diagnosis of AIFS on bedside biopsy by fine-needle aspiration cytology	FNAB demonstrated fungal hyphae in 8 of 9 patients, which was confirmed on permanent pathologic sections
Ghadiali[88]	2007	4	Retrospective review	14 patients who underwent bedside biopsy analyzed by frozen section, who were ultimately confirmed to have AIFS	Diagnostic accuracy of bedside biopsy by frozen section	Sensitivity 84% (95% CI, 0.52–0.96) with NPV 0.5 (95% CI, 0.12–0.88).
Gillespie[89]	2000	4	Prospective cohort	25 patients with clinical concern for AIFS, of whom 6 had confirmed AIFS on permanent pathology	Diagnostic accuracy of middle turbinate biopsy by frozen section	Sensitivity 75% (2 false negatives) and 100% specificity.
Abuzeid[87]	2022	5	Literature review[a]	Included 4 retrospective case series	Diagnosis of AIFS on bedside biopsy	Limited role in evaluation of AIFS.

[a]Downgraded due to review of 4 small case series.

of hyphae on frozen section or cytologic analysis does not confirm invasive disease, and in patients without obvious mucosal changes on nasal endoscopy a biopsy may be "random" leading to a false negative. It could be argued that, when obvious mucosal changes exist (e.g., discoloration or necrosis), the patient should proceed directly to the operating room for both tissue sampling and debridement. Nonetheless, when feasible, either endoscopic tissue biopsy or FNAB may help support the decision to initiative appropriate treatment. Table 11 summarizes evidence surrounding use of bedside biopsy for AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 4: 4 studies; Level 5: 1 study)
Benefit	Detection of fungal elements at the bedside can better inform the need for surgical debridement.
Harm	There is limited tissue sampling that can be performed given patient discomfort and associated comorbid conditions, which limit safe removal of tissue.
Cost	Direct costs are attributable to frozen section analysis. Biopsies obtained at the bedside and waiting for histopathologic analysis may delay operative debridement.

Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 6 studies)
Benefit–Harm Assessment	In cases where the diagnosis of AIFS is equivocal in an at-risk patient, bedside biopsies, particularly in abnormal tissue, may help gather more data in support of the decision to perform surgical debridement. This may be useful for diagnosis in patients who are unstable for surgery.
Value Judgments	Bedside biopsy may provide the most benefit when used to rule in AIFS, or when mucosal abnormalities can be sampled without significant bleeding risk or pain. FNAB serves as a minimally invasive alternative to endoscopic bedside biopsy, but may not yet be widely available.
Policy Level	Option: Bedside biopsy is an option in the workup of AIFS.
Intervention	Bedside biopsy may serve a role where mucosa can be sampled at the bedside with relative ease, but there is a risk of both false-negative and false-positive results. Care must be taken for patients at elevated risk for bleeding.

7 | IMAGING

Cross-sectional imaging with CT and MRI play vital roles as noninvasive diagnostic tests for the diagnosis

of AIFS, localize sites of infection to direct biopsy and extent of surgical debridement, and provide prognostic information.

Noncontrast CT of the paranasal sinuses is a common initial imaging modality used for assessment of AIFS given fast imaging time, no requirement for intravenous contrast administration, optimal evaluation of osseous structures, and capacity for surgical navigation. Many CT imaging findings have been implicated in AIFS, including unilateral nasal mucosal thickening (80% to 91%), periantral inflammation (22% to 38%), osseous erosion (0% to 57%), orbital involvement (13% to 28%), and intracranial extension (0% to 14%).[19,92,93] Silverman et al.[94] reported periantral inflammation without osseous erosion as potentially the earliest CT imaging finding of AIFS. DelGaudio et al.[93] found preantral inflammation (22%) and retroantral inflammation (9%) in a minority of their AIFS cases; however, these findings may have been underestimated as 11 of 23 patients had only coronal CT imaging. Additional CT findings in this study included unilateral nasal soft tissue thickening (91%), sinus mucoperiosteal thickening or opacification (91%), bone erosion (35%), and orbital invasion (26%), of which only unilateral nasal inflammation was a statistically significant finding. Given the relative low percentages of osseous erosion and extrasinus extension in their case series, DelGaudio et al. cautioned that these findings may be found late in the course of disease. More recently, Middlebrooks et al.[95] assessed 23 CT imaging parameters and designed a CT-based predictive tool utilizing bone dehiscence; septal ulceration; and periantral fat, orbit, pterygopalatine fossa, nasolacrimal duct, and lacrimal sac involvement, with presence of any one of these seven features resulting in 95% sensitivity, 86% specificity, 87% positive predictive value (PPV), and 95% negative predictive value (NPV) for AIFS.

Given its superiority in assessing soft tissue when compared with CT, MRI provides valuable information regarding enhancement characteristics of the sinonasal mucosa and is more sensitive in the detection of inflammation involving the extrasinonasal soft tissues, orbit, skull base, and intracranial contents. In 2010, Safder et al.[96] described the "black turbinate sign" of sinonasal tissue with lack of contrast enhancement (LoCE) on MRI corresponding to devitalized mucosa from angioinvasive hyphae. Lagos et al.[19] reported LoCE (75% sensitivity, 84% specificity), extrasinonasal extension (60% sensitivity, 89% specificity), and orbit compromise (50% sensitivity, 95% specificity) as MRI parameters significantly associated with AIFS. Although the "black turbinate sign" is highly specific for AIFS, Han et al.[97] caution it is not an uncommon imaging finding in immunocompetent patients without AIFS, but benign regions of nonenhancement in the nasal turbinates improve over subsequent series, have preserved thin peripheral enhancement, often have thin internal septa, and most frequently occur in the posterior inferior turbinates.

Many studies have also assessed LoCE on MRI for its prognostic value in the setting of AIFS.[98–101] Seo et al.[98] found LoCE on MRI in 17 of 23 (74%) of AIFS cases, with 13 of 23 (57%) having extrasinonasal LoCE. The 13 cases of AIFS with extrasinonasal LoCE had a 100% mortality. Kim et al.[99] used LoCE on preoperative MRI to determine surgical extent with residual or increasing extrasinonasal LoCE on postoperative MRI found in all, and only nonsurvivors in their series. In addition, Choi et al.[100] reported LoCE was an independent poor prognostic factor for disease-specific survival, and Nam et al.[101] reported LoCE of the skull base as an independent negative prognostic factor. As LoCE on MRI corresponds to devitalized tissue undergoing coagulative necrosis, consideration is given to surgical debridement of this tissue for disease clearance.

Groppo et al.[102] compared CT and MRI in patients who underwent operative endoscopy to rule out or diagnose AIFS. The authors found MRI to have better sensitivity than CT for the diagnosis of AIFS: 85% and 86% for MRI compared with 57% and 69% for CT for the two observers, respectively. However, the specificity (75% and 75% vs. 83% and 83%), PPV (92% and 92% vs. 89% and 90%), NPV (60% and 60% vs. 45% and 56%), and accuracy (82% and 83% vs. 65% and 74%) were similar for MRI and CT for the two observers, respectively. Given the finding of better sensitivity for the detection of AIFS, the authors concluded that contrast-enhanced MRI should be the initial screening imaging modality. In 2017, ACR Appropriateness Criteria Sinonasal Disease for evaluation of suspected IFS was revised to rate both MRI with and without IV contrast and CT without IV contrast as "usually appropriate" tests and stated: "MRI of the face and sinuses, including orbit and brain, is the study of choice. CT may be a complementary study and useful for surgical planning."[103] Table 12 summarizes evidence surrounding use of imaging for AIFS diagnosis.

TABLE 12 Imaging.

Study (first author)	Year	LOE	Study design	Study group(s)	Imaging modality	Major findings/outcomes
Lagos[19]	2021	3	Cohort study	50 immunocompromised patients with suspected AIFS	MR	LoCE: 75% sensitivity, 84% specificity, 50% PPV, and 94% NPV. Extrasinus extension: 60% sensitivity, 89% specificity, 60% PPV, and 89% NPV. Orbit compromise: 50% sensitivity, 95% specificity, 75% PPV, and 86% NPV. Healthy mucosa: 11% sensitivity, 34% specificity, 13% PPV, and 64% NPV. Positive serologic galactomannan: 40% sensitivity, 97% specificity, 67% PPV, and 91% NPV.
Nam[101]	2020	4	Case series	1) 37 surviving patients with AIFS 2) 13 nonsurviving patients with AIFS	MR	LoCE lesions in the orbit, cavernous sinus, infratemporal fossa, and meninges were significantly associated with AIFS-specific survival rate in univariate analysis, but not in multivariate analysis. In the multivariate analysis, only skull base with LoCE was an independent prognostic subsite ($p = 0.004$).
Choi[100]	2018	4	Case series	1) 12 surviving patients with AIFS 2) 11 nonsurviving patients with AIFS	MR	Variable enhancement patterns observed: LoCE (11 of 23, 48%), homogeneous (8 of 23, 35%), and heterogeneous (4 of 23, 17%). Patients with LoCE showed significantly lower survival rates vs. those without LoCE: 3 of 11 (27.2%) vs. 9 of 12 (75.0%), $p = 0.008$.
Kim[99]	2015	4	Case series	1) 16 surviving patients with AIFS 2) 5 nonsurviving patients with AIFS	MR	Preoperative extrasinonasal LoCE was observed in 8 of 16 survivors (50.0%), but in 4 of 5 nonsurvivors (80.0%). Postoperative extrasinonasal LoCE was significantly more common in nonsurvivors (5 of 5, 100%) than in survivors (0 of 16, 0%) ($p < 0.001$). Remnant lesions of extrasinonasal LoCE were not found in survivors. No significant differences between the intra- and extrasinonasal CE rates between survivors and nonsurvivors ($p = 0.119$ and $p = 0.111$, respectively).

(Continues)

TABLE 12 (Continued)

Study (first author)	Year	LOE	Study design	Study group(s)	Imaging modality	Major findings/outcomes
Middlebrooks[95]	2015	4	Retrospective case–control	1) 42 immunocompromised patients with AIFS 2) 42 immunocompromised patients without AIFS	CT	Two of the 7 variables (in a 7-variable model) predicted AIFS with 100% specificity. Eighty-eight percent of patients with AIFS presented with findings captured by ≥2 variables. The CT-based predictive model demonstrated 95% sensitivity (vs. 86%), 86% specificity (vs. 75%), and 95% NPV (vs. 60%) compared with previously published MR imaging data.
Seo[98]	2013	4	Case series	23 patients with AIFS	MR	Cervicofacial tissue infarct (CFTI), characterized as LoCE, may be relatively common MR finding of AIFS. CFTI detected in 17 of 23 patients (74%). Seventeen of 23 patients had intrasinonasal tissue infarct. Thirteen of 23 patients had extrasinonasal tissue infarct.
Groppo[102]	2011	4	Retrospective case–control	1) 17 immunocompromised patients with AIFS 2) 6 immunocompromised patients without AIFS	CT and MR	MR in detection of AIFS: 85–86% sensitivity, 75% specificity, 92% PPV, and 60% NPV. CT in detection of AIFS: 57–69% sensitivity, 83% specificity, 89–90% PPV, and 45–56% NPV. Extrasinus invasion most sensitive individual parameter in MR: 87–100% sensitivity. LoCE concordant with endoscopic mucosal findings 76.5% of the time.
DelGaudio[93]	2003	4	Retrospective case–control	1) 23 immunocompromised patients with AIFS 2) 10 control patients with AML and imaging evidence of sinusitis, but without AIFS	CT	Severe thickening of nasal cavity mucosa and soft tissues in 91% and bone erosion in 35%.
Saah[92]	2002	4	Case series	21 bone marrow transplant patients with AIFS	CT	Mucosal thickening seen in 67%, clear ethmoidal air cells amidst disease cells in 66%, hyperdense soft tissue mass in 71%, calcification in 1%, and bone destruction in 57%.
Silverman[94]	1998	4	Case series	1) 2 patients with AIFS 2) 112 patients without AIFS	CT	No controls had soft tissue infiltration in anterior periantral fat plane. One percent of controls with soft tissue infiltration in posterior periantral fat plane.

Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 9 studies)
Benefit	Noninvasive, high accuracy.
Harm	CT: low risk associated with radiation; MRI: low risk associated with gadolinium-based contrast agents; concern for treatment delay when awaiting for completion of imaging as imaging takes more time to be performed and interpreted.
Cost	MRI incurs higher economic and time costs than CT.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	Noninvasive tests are invaluable in initial screening of AIFS. Contrast-enhanced MRI is likely more sensitive for the detection of AIFS, better evaluates orbital and intracranial extent, and may provide prognostic information. CT is an acceptable alternative screening test and useful for surgical navigation.
Policy Level	Recommendation: Recommend contrast-enhanced MRI and CT.
Intervention	Contrast-enhanced MRI is recommended as a noninvasive screening test for AIFS, with CT as an acceptable alternative. Both imaging modalities play a complementary role in diagnosis.

8 | PATHOLOGY

8.1 | Frozen section evaluation

The utility of frozen sections has been evaluated for rapid diagnosis and for treatment planning for AIFS patients. A recent systematic review by Kim et al. identified an overall sensitivity of 83.3% and specificity of 98.6% based on the evaluation of nine total studies. Sensitivity was higher when evaluating patients with *Aspergillus* (81.0%) when compared with *Mucor* (75.4%).[104] This is in accord with other studies and is likely attributed to the decreased structural organization of *Mucor* compared with *Aspergillus*, making it more difficult to visualize on frozen sections. Subgroup analysis also showed higher diagnostic accuracy within the same patient as compared with individual specimens. Therefore, it was recommended to include multiple frozen specimens from a single case to reduce the likelihood of false-negative results.[104] Foshee et al. did not evaluate the diagnostic accuracy of frozen samples; the authors stated that frozen specimens are important for early diagnosis but are not routinely used to determine "clear margins."[105] They found no difference in mortality if fungus was present at the "margins" as long as debridement was performed on healthy, bleeding tissue. Two studies, which may have had overlapping specimens as they were conducted at the same institution, evaluated the use of periodic acid–Schiff (PASF) for frozen section (PASF-fs) staining.[106,107] This is discussed in more detail in a subsequent section ("Miscellaneous pathology staining techniques for diagnosis").

Overall, use of frozen specimens appears to be valuable as a means of rapidly and accurately identifying the presence of fungal elements and fungal invasion. Although adverse effects have not been directly studied, the specificity of an intraoperative frozen specimen is quite high, supporting that with its use there may be avoidance of unnecessary delayed or extended surgery. Although the side-effect profile associated with antifungal medications can be concerning, the risk of false-negative results on frozen sections is low, validating the need for this therapy if the frozen section identifies AIFS. Intraoperative frozen section evaluation for AIFS, on the other hand, particularly when used for "margin" assessment, is met with several technical and analytical challenges, which contribute to the relatively low sensitivity of this test. In their retrospective review of 309 frozen section specimens, Gonzalez et al. found an overall error rate of 15%.[108] Within the error group, 23.7% of cases were attributed to sampling errors (defined as fungus being present in permanent sections or when using special stains) and 76.3% were interpretive errors (a false-negative rate of 30% and a false-positive rate of 3%). Although sensitivity varies between existing studies, intraoperative frozen specimen results have the potential to aid in early diagnosis of this devastating problem. Table 13 summarizes evidence surrounding use of frozen sections for guiding AIFS diagnosis.

TABLE 13 Frozen sections.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kim[104]	2021	2	Systematic review/ meta-analysis of cohort studies	9 studies with 458 participants undergoing frozen section analysis for AIFS	Diagnostic accuracy of frozen sections for AIFS detection per patient and per specimen	Sensitivity 83.3%, specificity 98.6%, and PPV 98.2%.
Alkhateb[109]	2021	4	Retrospective review	48 patients with 133 intraoperative frozen section specimen evaluations for AIFS	Diagnostic accuracy of intraoperative frozen sections	Sensitivity 88.5%, specificity 100%, PPV 100%, and NPV 90.6%.
Gonzalez[108]	2021	4	Retrospective review	202 cases of AIFS from 104 patients, 309 intraoperative specimens from AIFS patients	Evaluation of errors on final pathology review	Fifteen percent significant errors in the 309 blocks; of these errors, 30% did not identify fungus and only 3% overcalled the presence of fungus.
Crist[107]	2019	4	Retrospective review	146 patients with 271 frozen section specimens	Diagnostic accuracy of intraoperative frozen sections (H&E staining vs. PASF-fs staining)	H&E-fs sensitivity 81% and specificity 97%. PASF-fs sensitivity 98% and specificity 100%
Silveira[63]	2019	4	Retrospective review	46 patients, 32 frozen specimens from suspected AIFS patients	Diagnostic accuracy of intraoperative frozen sections	Sensitivity 90.6% and specificity 72.7%.
Hennessey[a106]	2018	4	Retrospective/ prospective cohort	124 patients, 271 frozen specimens, analysis was calculated per patient	Diagnostic accuracy of intraoperative frozen sections (H&E-fs vs. PAFS-fs staining)	H&E-fs sensitivity 83%, improved to 95% with PAFS-fs staining, and specificity 100%.
Melancon[110]	2017	4	Retrospective review	31 frozen sections from 28 patients undergoing surgery for acute AIFS	Diagnostic accuracy of intraoperative frozen sections	Sensitivity 87.5%, specificity 100%, NPV 70%, and PPV 100%.

(Continues)

TABLE 13 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Papagiannopoulos[111]	2017	4	Retrospective review	18 patients undergoing surgery for AIFS with evaluation of 66 frozen specimens	Diagnostic accuracy of intraoperative frozen sections	Sensitivity 72.7%, specificity 100%, PPV 100%, and NPV 64.7%.
Foshee[105]	2016	4	Retrospective review	27 patients with intraoperative frozen section evaluations for AIFS	Differences in mortality between positive and negative margins on frozen sections for fungal elements	No difference in mortality between those with positive and negative margins on frozen sections after surgical resection.
Taxy[112]	2009	4	Retrospective review	12 patients with AIFS, 8 patients with frozen sections performed	Diagnostic accuracy of intraoperative frozen sections (stained with H&E and rapid Romanowsky stain)	Sensitivity 62.5% and specificity 100%.
Ghadiali[88]	2007	4	Retrospective review	Six patients with intraoperative frozen sections for AIFS	Diagnostic accuracy of intraoperative frozen sections	Sensitivity 84%, specificity 100%, NPV 79%, and PPV 100%.
Hofman[113]	2003	4	Retrospective review	12 patients with AIFS and 7 patients with frozen sections performed	Diagnostic accuracy of intraoperative frozen sections (stained with toluidine blue, Gomori–Grocott methanmine silver, H&E, and PAS)	Sensitivity 85.7% and specificity 100%.

[a]Study included both intraoperative and bedside frozen specimens.

Aggregate Grade of Evidence	C (Level 2: 1 study; Level 4: 11 studies)
Benefit	Rapid and timely diagnosis for treatment planning, especially for disease known for rapid progression as well as intraoperative disease mapping, which provides additional prognostic information.
Harm	Possible delay of treatment pending frozen section interpretation for diagnosis. Risk of incorrect diagnosis or incomplete resection due to false negatives, with increased intraoperative time.
Cost	Direct and indirect costs of increased operative time, and direct cost for real-time pathologic interpretation.
Benefit–Harm Assessment	Likely benefit over harm.
Value Judgments	Although sensitivity and negative predictive value vary among studies, frozen sections have a high positive predictive value and specificity, supporting timely diagnosis and subsequent treatment with surgical debridement and antifungal medications.
Policy Level	Recommendation: The use of frozen sections is reasonable for initial diagnosis given its high positive predictive value.
Intervention	Preoperative and intraoperative frozen evaluation is associated with high positive predictive value and potential for avoidance of surgical/treatment delays and may provide advantages for guiding treatment and for prognostic information.

8.2 | Miscellaneous pathology staining techniques for diagnosis

Various histopathologic evaluations other than frozen sections have been reported in the literature as potentially accurate, efficient means of identifying AIFS. Several small studies have evaluated the utility of special stains and evaluations of pathology sections. Montone et al.[65] and Myoken et al.[114] evaluated in situ hybridization for identification of fungal species, proposing an alternative method for patients with culture-negative results. Similarly, Chatarantabut et al.[115] proposed the use of PCR as a faster, potentially more accurate way of identifying fungal species, but they reported a low sensitivity for this method.

Currently, the "gold standard" for permanent section analysis is hematoxylin–eosin (H&E) staining, and there is no accepted or widely used alternative method. Additional studies, such as PASF, DiffQuik (DQ), and maspin staining, may aid in the diagnosis of AIFS on either frozen or permanent pathologic sections, but these are currently considered adjuncts and their use is inconsistent across institutions. Modified PAS staining for frozen sections was able to identify fungus not otherwise visible on frozen section H&E, decreasing the false-negative rate and improving diagnostic accuracy in studies by Hennessey et al.[106] and Crist et al.[107] Another readily available stain, the DQ stain, was also incorporated into a frozen section protocol by Gonzalez et al.,[108] where the authors observed that DQ staining subjectively improved the appearance of fungal hyphae, with improved characterization of morphology and presence of septations. DQ staining was also performed more rapidly (5 minutes) in their experience when compared with the PAS protocol (20 to 25 minutes) described by Crist et al.[107] Last, maspin staining has been shown to be significantly decreased in cases of fungal sinusitis, and to an even greater degree in AIFS, with a relatively good sensitivity (92%).[116] It also may serve as a biomarker of invasion as maspin plays a role in maintaining intercellular adhesion and basement membrane integrity in oncologic studies. Table 14 summarizes evidence surrounding use of other staining techniques for guiding AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 4: 8 studies)
Benefit	Potentially improved sensitivity for intraoperative frozen assessment using PAS stain during frozen section and potentially improved fungal identification in culture-negative specimens using ISH.
Harm	Risk of false-negative results.
Cost	Indirect cost related to increased utilization of different staining agents/processes, time of additional workup.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Although these methodologies are new and not well studied, they may provide slightly improved frozen section sensitivity and fungal species identification when compared with currently accepted techniques.
Policy Level	Option: The use of supplemental methodologies is an option for potential decreased time to diagnosis and fungal species identification, leading to improved surgical and medical intervention.
Intervention	The methods just described may be considered in addition to the current practice of tissue fungal cultures, H&E frozen section, and permanent analysis, but should not be used as the primary technique for diagnosis, due to lack of sufficient research.

TABLE 14 Miscellaneous pathology staining techniques for diagnosis.

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Gonzalez[108]	2021	4	Prospective cohort	202 cases of AIFS from 104 patients, 309 intraoperative specimens from AIFS patients, 16 specimens where DiffQuik staining was used over a 1-year trial period	Diagnostic accuracy of intraoperative frozen sections (DiffQuik staining)	DiffQuik sensitivity 83% and specificity 100%.
Chatarantabut[115]	2020	4	Retrospective review	81 samples; only 64 samples with adequate DNA from tissue blocks of patients with AIFS patients	Evaluation of polymerase chain reaction technique for detection of fungal species in formalin-fixed specimens	Thirty-one percent of samples yielded PCR products for sequencing, and they were able to identify the fungal genus.
Crist[107]	2019	4	Prospective cohort	146 patients with 271 frozen section specimens	Diagnostic accuracy of intraoperative frozen sections (PAS-fs staining)	Sensitivity 98% and specificity 100%.
Hennessey[a][106]	2018	4	Retrospective/ prospective	124 patients, 271 frozen specimens; analysis was calculated per patient	Diagnostic accuracy of intraoperative frozen sections (H&E-fs vs. PAFS-fs staining)	H&E-fs sensitivity 83%, improving to 95% with PAFS-fs staining, with specificity 100%.
Schuman[117]	2018	4	Retrospective review	13 AIFS patients	Diagnostic accuracy of touch preparation (an alternative histologic method to frozen section) with DiffQuik staining method for detection of AIFS	Sensitivity 56%, specificity 100%, PPV 100%, and NPV 67%.
Huang[116]	2017	4	Retrospective case–control	12 cases of AIFS, 30 cases of noninvasive fungal sinusitis, with 30 CRS patients as controls	Evaluation of IHC staining for anti-maspin polyclonal antibody for diagnosis of fungal sinusitis	Maspin expression was downregulated in fungal sinusitis compared with CRS, and lowest in AIFS specimens. A maspin-staining score with a cutoff of 5.7 had a 92% sensitivity and 88% specificity for diagnosis of AIFS.
Montone[65]	2011	4	Retrospective review	55 specimens from 23 patients with AIFS	Evaluation of in situ hybridization with biotin-labeled probes targeting *Aspergillus* sp., *Fusarium* sp., and *Rhizopous* sp.	Sixty percent of AIFS cases had nucleic acid preservation. ISH-positive results possibly aid in species differentiation in culture-negative patients.
Piao et al.[118]	2008	4	Retrospective review	89 fungal sinusitis specimens, 28 of which were AIFS	Evaluation of MUC5B, MUC2, and MUC5AC antibody staining for detection of fungus	MUC5B detected 100% *C albicans*, 91% *Aspergillus*, and 0% *Mucorales*.

[a]Study included both intraoperative and bedside frozen specimens.

TABLE 15 Outcomes related to surgery vs. no surgery.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Vaughan[35]	2018	2	Systematic review and meta-analysis	175 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Overall survival of 59.5%. However, patients who did not have surgery had survival of only 21%, suggesting a survival benefit in those receiving surgery.
Turner[4]	2013	2	Systematic review	807 patients with AIFS	Overall survival	Surgery significantly improved survival compared with no surgery.
Sun[120]	2010	3	Cohort study + systematic review	90 solid-organ transplant recipients with rhino-orbito-cerebral mucormycosis	Overall survival	Improved survival with surgery + amphotericin compared with amphotericin and no surgery.
Jung[121]	2009	3	Cohort study	12 patients with rhinocerebral mucormycosis	Overall survival	Seventy percent of operated patients recovered, whereas only 1 of 2 (50%) patients without surgery recovered.
Bhansali[45]	2004	3	Cohort study	35 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Treatment without surgery (i.e., amphotericin alone) significantly worsened survival.
Blitzer[54]	1980	3	Systematic review	170 cases of paranasal sinus mucormycosis	Overall survival	Surgery compared with biopsy alone or no surgery significantly improved survival.
Chen[68]	2011	4	Cohort study	110 cases of invasive fungal sinusitis	Overall survival	Surgical debridement significantly improved survival compared with no surgery.

9 | SURGERY

Surgery has become an essential component in the management of AIFS and is the mainstay for removal of infected and necrotic tissue.[119] The extent of surgical dissection has been guided largely by the tenet of debridement until the visualization of healthy, bleeding tissue.[119] Recent publications have continued to explore the impact of additional strategies on optimizing complete surgical removal and improving clinical outcomes, including the impact of surgical timing and early intervention, the initial extent of surgery, the role of different surgical approaches, and decisions aiding return to the operating room (OR). This section comprehensively addresses these important aspects of the surgical planning and management of AIFS.

9.1 | Survival with surgery vs. no surgery

An association between surgery and improved survival in patients with AIFS has been consistently reported.[4,35,45,54,68,120,121] Earlier reports have suggested surgery provides improved survival outcomes compared with no surgery.[4,35,54,68,121] In addition, combination therapy with surgery and medical treatment has been reported to confer improved survival when compared with medical treatment alone.[45,120] Table 15 summarizes evidence surrounding outcomes of surgery vs. no surgery in AIFS.

Aggregate Grade of Evidence	C (Level 2: 2 studies; Level 3: 4 studies, Level 4: 1 study)
Benefit	Surgery improves survival compared with no surgery; intraoperative assessment of extent of disease may inform care globally.
Harm	Risks associated with surgery, potential disfigurement from external approaches, and medical factors complicating surgical risks (e.g., thrombocytopenia increasing risk of hemorrhage).
Cost	Cost of procedure must be weighed with costs of entire hospitalization with and without surgery.
Benefit–Harm Assessment	Preponderance of benefit over harm depending on medical condition.
Value Judgments	This is a rare disease with a paucity of evidence investigating the impact of timing of surgical treatment and extent of surgical debridement on survival outcomes; however, whenever debridement is undertaken, there appears to be consistent evidence of survival benefit. The literature tends to be skewed toward reporting cases treated with surgery.
Policy Level	Recommendation: Surgical intervention is recommended.
Intervention	Surgical debridement of infected/necrotic tissue should be considered in patients with AIFS, if considered an appropriate surgical candidate.

9.2 | Surgical timing and impact of early intervention

Traditionally, AIFS has been considered a surgical emergency and a "race against time." Several studies have investigated the importance of surgical timing on outcomes in patients with AIFS.[20,23,35,45,48,51,54,121–126] Of the 13 studies identified, 8 reported improved survival with early treatment, 3 studies demonstrated no difference, and 1 study reported improved outcomes with late treatment.[20,23,35,45,51,54,121–126] Separately, Kennedy et al. reported that most patients with a longer time from symptom onset to diagnosis required more extensive surgery than those diagnosed earlier.[48] Although these combined findings suggest a role for early surgical intervention, optimal time to treatment remains unclear, as cutoffs for early intervention ranged from 4 to 16 days.[20,23,45,51,122–124,126] This finding is likely in part due to the differing methods of defining optimal time to surgery, with some studies using time from symptom onset to surgery and others from histopathologic diagnosis to surgery. To date, there is no evidence to guide emergent (i.e., as soon as possible) vs. urgent (i.e., waiting until the next day) surgical treatment for AIFS, and the impact of time from symptom onset to time of intervention. Table 16 summarizes evidence surrounding timing of surgery in AIFS.

Aggregate Grade of Evidence	C (Level 2: 1 study; Level 3: 9 studies, Level 4: 3 studies)
Benefit	Early surgical intervention may improve survival outcomes and limit disease progression.
Harm	Emergent surgery status precludes appropriate preoperative optimization and surgeon/facility preparation.
Cost	Theoretically increased costs of emergent/urgent surgical utilization.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Studies demonstrating improved survival with early surgical treatment vary on the critical time from symptom onset/diagnosis to treatment. Given the aggressive nature of the disease and its associated high mortality rates, it is prudent to consider timely surgery if medical condition permits.
Policy Level	Option: Option for emergent intervention, although there are no clear data to guide early emergent vs. urgent surgical intervention (or timing in general).
Intervention	Early surgical intervention may benefit patients with AIFS. The optimal time from symptom onset to surgery remains unclear.

9.3 | Initial extent of surgery

Guidelines to help determine appropriate extent of initial surgical resection have not been established.[6,32,36,38,88,89,113,125,127–129] Preliminary reports discussed the use of preoperative imaging demonstrating extent of disease involvement; intraoperative visualization of healthy, bleeding tissue; and intraoperative margin assessment using frozen sections to assist with the extent of initial resection.[6,21,38,89,105,125,128–133] Those studies reported that complete surgical resection improves survival when compared with incomplete resection.[6,89] However, the studies did not report the resectability of the disease, which would be a confounding factor in guiding extent of resection. Future studies are needed to determine each method's ability to accurately guide initial extent of surgery, along with their impact on disease progression,

TABLE 16 Surgical timing and impact of early intervention.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Vaughan[35]	2018	2	Systematic review and meta-analysis	140 studies with 175 total patients receiving treatment for rhino-orbito-cerebral mucormycosis	Overall survival	Overall survival for patients surgically treated for 1–6 days, 7–12 days, and 13–30 days from symptom onset was 61%, 50%, and 75%, respectively.
Alejandro[20]	2020	3	Cohort study	18 pediatric patients with AIFS	Overall survival	Overall survival was significantly lower in patients who received surgery >7 days after initial diagnosis.
Fernandez[23]	2018	3	Cohort study	19 patients receiving treatment for surgical pathology-confirmed AIFS	Impact of different variables on survival, including treatment delay (defined as time from the first symptom of AIFS), increased serum galactomannan level, or suspect findings on sinus CT scan (in case of asymptomatic patients) to surgical treatment) on survival	Treatment delay >4 days significantly decreased survival.
Jeong[124]	2015	3	Cohort study	24 histologically proven cases of invasive mucormycosis (13 of 24 with rhino-orbito-cerebral mucormycosis)	Overall survival	Time to treatment significantly increased mortality on univariate analysis ($p = 0.045$). The only significant predictor of decreased survival on multivariate analysis was a delayed diagnostic procedure of >16 days ($p = 0.012$).
Saedi[125]	2011	3	Cohort study	30 patients with rhino-cerebral mucormycosis (patients with central nervous system involvement, extensive orbital involvement, and palatal necrosis were excluded)	Overall survival	Time delay between diagnosis and treatment did not significantly impact survival. The authors did not wait for pathologically or biologically confirmed diagnosis to start surgery in cases.
Jung[121]	2009	3	Cohort study	12 patients undergoing treatment for rhino-cerebral mucormycosis	Overall survival	Time from histopathologic diagnosis to surgery ranged from 1 to 25 days. All 3 patients with surgery after 7 days survived (100%). Three of 7 patients who had surgery within 7 days died (43%). Of the 2 patients who had surgery, 1 recovered with medical therapy alone (50%).

(Continues)

TABLE 16 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Mohindra[126]	2007	3	Cohort study	27 patients with rhino-cerebral mucormycosis	Overall survival	Early diagnosis (within 2 weeks of symptom onset) and subsequent earlier treatment led to 78.6% patient survival compared with 53.8% in those with delayed diagnosis and subsequently delayed treatment.
Bhansali[45]	2004	3	Cohort study	31 diabetic patients with rhino-orbito-cerebral mucormycosis; 26 of these patients received surgery + amphotericin, whereas 5 received amphotericin alone	Overall survival	Delayed diagnosis and treatment ($p < 0.05$) conferred worse overall survival.
Khor[123]	2003	3	Cohort study	21 patients with rhino-cerebral mucormycosis; 16 received medical and surgical whereas 5 received medical therapy alone with amphotericin B	Overall survival[a]	Four patients had delayed diagnosis and treatment. Delayed diagnosis and treatment were significantly lower in those who recovered (1 of 16) vs. those who died (3 of 5) ($p = 0.028$).
Blitzer[54]	1980	3	Retrospective review + systematic review	179 cases of paranasal sinus mucormycosis	Overall survival	Effect of time between diagnosis and surgery (in 77 patients receiving surgery) was as follows: day $\leq 7 = 60\%$ survival, and day $>7 = 81\%$ survival.[b]
Piromchai[122]	2014	4	Cohort study	59 patients with AIFS ($n = 45$) and chronic AIFS ($n = 14$) receiving surgical treatment before and after 14 days from symptom onset from 1997 to 2008	Overall survival	Treatment within 14 days of symptom onset significantly increased survival.
Kennedy[48]	1997	4	Cohort study	26 patients with AIFS	Association of delayed treatment on disease extent	Patients requiring extensive surgery had significantly longer time from symptom onset to diagnosis and significantly more sites involved vs. those with limited surgery.
Yohai[51]	1994	4	Systematic review of case reports	145 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Delay in time from first symptom to surgical treatment began to decline after 6 days, with survival rates of 1–6 days, 7–12 days, and 13–30 days in 81%, 52%, and 42% of patients, respectively.

[a]Delayed diagnosis not defined in abstract.
[b]Time from diagnosis to surgery was unspecified in 31 cases.

recurrence, surgical morbidity, and overall survival. Table 17 summarizes evidence surrounding initial extent of surgery in AIFS.

Aggregate Grade of Evidence	C (Level 3: 3 studies; Level 4: 7 studies)
Benefit	Increases likelihood of complete surgical resection, decreases resection of nondiseased tissue, and there are fewer explorations with more comprehensive upfront surgery.
Harm	Over-resection of potentially uninvolved tissue.
Cost	Minimal—increased OR time with frozen sections.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	Complete surgical resection and local control appears to provide survival benefit. Evidence on preoperative imaging to assist with surgical planning and surgical resection to healthy tissue suggests these strategies may reduce recurrence. However, this evidence is limited. In addition, there is limited evidence suggesting intraoperative frozen sections can help guide the extent of surgical resection; impact on survival is unclear. Future studies are required to assess the role of these interventions on outcomes.
Policy Level	Option: Option for aggressive initial debridement as opposed to targeted surgery.
Intervention	Determine disease extent on preoperative imaging findings; resection of tissue until healthy, bleeding tissue is observed; and consider frozen sections of surgical margins to assist with extent of resection.

9.4 | Role of extended surgical approaches

The use of extended endoscopic surgery includes medial maxillectomy, advanced frontal sinus approaches (e.g., Draf III), and dissection/debridement of the pterygomaxillary and infratemporal fossae. Evidence of the impact of these approaches on survival is limited. However, preliminary evidence suggests extended approaches could prevent disease progression and recurrence, and may therefore provide improved survival outcomes, particularly with extended maxillary sinus and pterygopalatine fossa surgery.[38,121,129,133–136] The impact of advanced frontal sinus surgery on survival in patients with AIFS has not been reported. Table 18 summarizes evidence surrounding extended surgical approaches in AIFS.

Aggregate Grade of Evidence	C (Level 3: 4 studies; Level 4: 3 studies)
Benefit	Increases likelihood of complete surgical resection in select cases where conventional techniques may not be sufficient.
Harm	Unique surgical risks associated with extended approaches (e.g., palatal numbness with pterygopalatine fossa dissection).
Cost	Increased technical expertise and equipment (e.g., drills) and increased operative time.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Evidence suggests select patients requiring extended endoscopic approaches have low rates of disease recurrence. Many extended approaches may be performed safely in a minimally invasive manner.
Policy Level	Option: Option for extended endoscopic approaches for AIFS.
Intervention	Extended endoscopic surgical approaches (e.g., pterygopalatine/infratemporal fossa dissection, modified Lothrop) may be helpful adjuncts in removal of all diseased tissue.

9.5 | Evidence for open maxillectomy/resection

Open maxillectomy has been reported in cases determined not amenable to endoscopic resection.[137–141] The rate of survival in patients undergoing open maxillectomy is highly variable, suggesting significant variability in outcomes based on the nature of the condition.[137–141] Studies by Ramadorai et al. and Ardeshipour et al. showed favorable outcomes, with survival rates of 90% and 100%, respectively.[139,141] In addition, the lone survivor undergoing open maxillectomy in the study by El-Naaj et al. had the most extensive disease, suggesting additional factors that may play a role in survival in patients undergoing open maxillectomy.[137] Table 19 summarizes evidence surrounding open resection in AIFS.

TABLE 17 Initial extent of surgery.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Payne[38]	2016	3	Cohort study	41 patients with AIFS receiving treatment from 1999 to 2014	Overall survival	All 37 patients undergoing surgery were debrided until healthy, bleeding tissue was encountered in all cases during initial surgery. Nine patients required second operations and 39% died before discharge.
Saedi[125]	2011	3	Cohort study	30 patients with rhinocerebral mucormycosis (patients with central nervous system involvement, extensive orbital involvement, and palatal necrosis were excluded); the authors used preoperative endoscopy, imaging, surgical resection to the level of viable tissue, opening of all involved sinuses to allow for fungus drainage, and frozen section analysis of suspicious tissue to guide initial extent of surgery	1) Overall survival 2) Recurrence	Recurrence occurred in 10% of patients. Overall survival was 60%
Eliashar[127]	2007	3	Cohort study	14 bone marrow transplantation patients with sinonasal invasive aspergillosis. All patients received a standardized preoperative and intraoperative protocol, part of which included surgical planning with CT (navigation system or regular high-resolution CT) and debridement until bleeding normal tissue appeared	1) Survival 2) Recurrence	Six patients died secondary to primary disease or comorbidities. There was no evidence of residual disease in any of the patients.
Fadda[32]	2021	4	Case series	4 patients with AIFS	Correlate AIFS with underlying symptoms, imaging and surgical findings, and treatment	All 4 patients received endoscopic sinus surgery with complete removal of all necrotic tissue. Three had extra-sinonasal extension. Seventy-five percent of patients were alive at 13 months.

(Continues)

TABLE 17 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Roxbury[6]	2017	4	Case series	19 patients receiving treatment for surgical pathology-confirmed AIFS	Impact of complete surgical resection, as defined by negative surgical margins on intraoperative frozen sections or no evidence of disease on postoperative endoscopy, on short-term survival (i.e., survival until hospital discharge)	Patients with complete surgical resection of disease had higher rates of short-term survival (95.5%) vs. those with incomplete resection (42.9%).
Ergun[36]	2017	4	Case series	19 cases with AIFS; surgical debridement until healthy, bleeding tissue was identified in all cases	Overall survival	Overall survival was 38.8%.
Taxy[128]	2009	4	Case series	8 patients with acute fungal sinusitis undergoing intraoperative frozen section analysis to guide extent of surgical debridement	Sensitivity of frozen sections	Sensitivity of frozen sections seen in 62.5% of patients. All patients in this cohort died.
Goyal[129]	2009	4	Case series	4 AIFS patients with infratemporal fossa extension undergoing resection via an endonasal endoscopic approach through the sphenopalatine foramen ± the assistance of CT-based navigation	Recurrence in the infratemporal fossa	The use of intraoperative computerized navigation can help determine the extent of surgical resection required. Two patients were lost to follow-up. One patient died of graft-vs-host disease. No patients had evidence of recurrence in the infratemporal fossa on follow-up.
Hofman[113]	2003	4	Case series	3 rhino-cerebral mucormuycosis patients undergoing intraoperative frozen section analysis to guide extent of surgical debridement	Impact of frozen sections on surgical resection	Frozen sections allowed radical surgical excision of all infected tissue and guided the need for orbital exenteration in 2 cases.
Gillespie[89]	1998	4	Cohort study	25 patients treated for AIFS	Impact of completeness of surgical resection, as defined by operative reports noting healthy bleeding tissue and postoperative surgical margins, on overall survival	Completeness of surgical resection significantly increased overall survival (90% vs. 0%).

TABLE 18 Role of extended surgical approaches.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Prado-Calleros[134]	2016	3	Cohort study	15 patients with rhino-orbital mucormycosis (all involving pterygomaxillary fossa on imaging); 7 patients (historic group A) received endoscopic or combined endoscopic and external surgery, whereas the remaining 8 patients (group B) received endoscopic resection with empiric medial maxillectomy and pterygomaxillary fossa exploration ± orbital exenteration	Overall survival	Group B patients receiving endoscopic resection with empiric medial maxillectomy and pterygomaxillary fossa exploration survived, whereas group A had a survival rate of 50%.
Kasapoglu[133]	2010	3	Cohort study	22 patients with AIFS receiving endoscopic ($n = 19$) or open ($n = 7$) surgical resection	Overall survival	The only patient undergoing an extended endoscopic approach with medial maxillectomy died on day 7 of hospitalization.
Jung[121]	2009	3	Cohort study	12 patients with rhino-cerebral mucormycosis	Overall survival	The 1 patient receiving extended endoscopic resection with medial maxillectomy survived.
Mohindra[126]	2007	3	Cohort study	27 patients with rhino-cerebral mucormycosis	Overall survival	The 2 patients receiving medial maxillectomy remained alive at the end of the study.
Hernandez[136]	2015	4	Case series	5 cases of rhino-orbito-cerebral mucormycosis	Overall survival	All 5 patients with extended endoscopic resection into pterygomaxillary fossa survived.
Goyal[129]	2009	4	Case series	4 AIFS patients with infratemporal fossa extension undergoing resection via an endonasal endoscopic approach through the sphenopalatine foramen with or without the assistance of CT-based navigation	Recurrence in the infratemporal fossa	The transnasal endoscopic approach allowed for excellent exposure to the infratemporal fossa. Two patients were lost to follow-up. One patient died from graft-vs-host disease. No patients had evidence of recurrence in the infratemporal fossa on follow-up.
Jiang[135]	1999	4	Cohort study	18 patients with rhinocerebral mucormycosis treated with endoscopic sinus surgery, open approaches, or both	Overall survival	The patient receiving extended endoscopic sinus surgery (Denker) was alive at study completion.

TABLE 19 Role of open maxillectomy/resection.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ramadorai[139]	2019	4	Case series	10 patients with rhino-cerebral mucormycosis undergoing open maxillectomy	Disease-free survival	Nine of 10 patients were disease-free and alive at 6 months.
Ardeshirpour[141]	2014	4	Cohort study	11 pediatric patients with AIFS	1) Disease recurrence 2) Overall survival	All 8 patients undergoing open maxillectomy were cured of their fungal disease.
El-Naaj[137]	2013	4	Case series	6 cases of rhino-cerebral mucormycosis receiving subtotal ($n = 3$) and total ($n = 3$) maxillectomy	Overall survival	Overall survival in this cohort was 16.6%. Only 1 patient died as a direct result mucormycosis, whereas the other 4 died of their underlying illness. The lone survivor had the most extensive disease, suggesting open maxillectomy can prevent recurrence when indicated.
Ketenci[138]	2011	4	Cohort study	14 patients with rhino-cerebral mucormycosis	Overall survival	All 8 patients undergoing open maxillectomy died within 5 weeks.
Abedi[140]	1984	4	Cohort study	18 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Seven of 11 patients undergoing open medial maxillectomy survived (63.6%).

Aggregate Grade of Evidence	C (Level 4: 5 studies)
Benefit	Increases likelihood of complete surgical resection, particularly when the palate, external nose, and premaxillary soft tissues are involved.
Harm	Increases morbidity, aesthetic deformity, and residual functional defects, with uncertain survival benefit.
Cost	Costs of rehabilitation (e.g., obturator, free flap reconstruction).
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	Open maxillectomy appears to be an acceptable option to achieve complete resection in patients requiring extensive surgical resection that is not amenable to endoscopic approach.
Policy Level	Option: Open maxillectomy is an option for AIFS.
Intervention	Consider open maxillectomy for patients with disease extension that cannot be treated with endoscopic surgery alone, such as involvement of the palate and premaxillary soft tissues.

9.6 | Survival outcomes for open vs. endoscopic approaches

The appropriate surgical approach remains unclear in many patients with AIFS. Alejandro et al. reported no survival differences between open, endoscopic, and combined approaches.[20] A systematic review by Turner et al. and a retrospective review by Kasapoglu et al. reported improved survival with endoscopic compared with open resection.[4,133] In contrast, a case series by Sohail et al. found improved survival in patients undergoing a combined approach compared with endoscopic surgery alone.[142] When considering the differences in survival between approaches, it is important to acknowledge biases that may exist between open and endoscopic surgery. For instance, patients with limited disease may be amenable to endoscopic surgery. In addition, patients undergoing open approaches may have more extensive disease upfront and, therefore, worse outcomes, regardless of approach. Alternatively, these patients undergoing an open approach may have more extensive resection in certain cases, leading to improved outcomes compared with the endoscopic approach at the expense of higher postoperative morbidity. Without strong evidence to suggest that an open approach consistently provides superior outcomes, future studies controlling for patient disease factors, including disease

location and extent, organisms involved, and host immunity status, are required to better understand the optimal role of each approach. Table 20 summarizes evidence surrounding open vs. endoscopic surgical approaches for AIFS.

Aggregate Grade of Evidence	C (Level 2: 1 study; Level 3: 2 studies; Level 4: 1 study)
Benefit	Endoscopic: Improved visualization, minimally invasive approach. Open: Direct access, improved vascular control.
Harm	Endoscopic: Inability to clear certain areas (e.g., premaxillary soft tissues, palate). Open: Risk of over-resection, decreased visualization, and aesthetic and functional sequelae.
Cost	Endoscopic equipment and technical expertise.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	Studies reported improved or similar survival rates with endoscopic compared with open resection. Reasons for this may include increased disease progression in cases requiring open surgery. Endoscopic approaches should be considered in all cases as primary surgical treatment. However, given evidence that open approaches can provide similar survival outcomes compared with endoscopic approaches, it is recommended to perform open or combined procedures in select cases whenever diseased tissue cannot be completely removed through endoscopic approaches.
Policy Level	Recommendation: Endoscopic surgery recommended when indicated.
Intervention	It is reasonable to consider endoscopic resection whenever possible, and to consider combined or open surgery in more advanced cases that are not amenable to complete resection with endoscopic techniques.

9.7 | Scheduled return to OR

Optimal survival of AIFS requires local surgical control, medical therapy, and reversal of underlying factors.[4,6,36,89] To improve local control and completely resect recurrent or incompletely removed tissue, multiple surgeries are often required.[21,33,63,143–146] The number of surgeries reported per patient has ranged from 1 to 7, with variations in

TABLE 20 Survival outcomes between open and endoscopic approaches in AIFS patients.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Turner[4]	2013	2	Systematic review	807 patients with AIFS	Overall survival	Patients who underwent endoscopic resection had improved survival (63.54%) compared with those who received open surgery (54.08%).
Alejandro[20]	2020	3	Cohort study	18 pediatric patients with AIFS	Overall survival	No difference in survival between open, endoscopic, and combined approaches.
Kasapoglu[133]	2010	3	Cohort study	26 patients with AIFS	Disease-specific survival	Disease-specific survival was 90% (9 of 10) and 57.1% (4 of 7) for endoscopic and open surgery groups, respectively.
Sohail[47]	2001	4	Case series	9 patients with AIFS receiving open or combined open and endoscopic approaches	Overall survival	Overall survival in 3 patients with combined approach were alive (100%) compared with 3 of 4 patients receiving endoscopic approach alone.

time to repeat surgery based on patient factors and clinical judgment (range, 1 to 76 days).[21,32,33,127,145,146] In addition, Kashkouli et al., Tarkan et al., Silveira et al., and Wu et al. reported conflicting evidence on the impact of multiple surgeries on survival.[33,63,146–148] In patients undergoing repeat surgery, factors including postoperative endoscopy, postoperative imaging, and assessment of tissue pathology margins have been reported to assist with the decision to return to surgery.[33,63,125,143–149] Future studies should assess the impact on recurrence and survival of each technique used to aid in the decision to return to the OR. Table 21 summarizes evidence surrounding scheduled returns to the OR for AIFS.

Aggregate Grade of Evidence	C (Level 3: 9 studies; Level 4: 4 studies)
Benefit	Timely re-evaluation of disease progression and improved local control as needed. Additional benefits include characterization and debridement of additional involved tissue.
Harm	Unnecessary repeat surgical debridement or anesthesia time and risk of damage to uninvolved intracranial or intraorbital structures.
Cost	Increased costs with additional procedures.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	AIFS is a disease with high mortality and rapid progression. Given reports of improved survival with complete local control, methods to monitor completeness of surgical resection and the need for OR return (i.e., postoperative endoscopy and postoperative monitoring of permanent section tissue margins) are recommended. Patient-specific risk factors (e.g., diabetes mellitus or hematologic malignancy) and the involved fungal organisms may also affect the context and subsequent risk for disease progression necessitating return to the OR for a "second look."
Policy Level	Recommendation: Return to OR recommended when clinically appropriate.
Intervention	Use postoperative infection parameters (e.g., fevers, complete blood counts, C-reactive protein, etc.), clinical exam/symptoms (e.g., pain), follow-up imaging, nasal endoscopy, and histopathology of permanent section surgical margins to guide decision if/when return to OR is indicated.

10 | MEDICAL THERAPY

10.1 | Systemic antifungals

Systemic antifungal therapy represents one of the pillars of management of AIFS. However, limited data exist comparing types of antifungals employed specifically among patients who have AIFS. Many of the treatment principles have been extrapolated from data published comparing antifungals among patients with invasive fungal infections in general. Furthermore, many of the available studies did not analyze patients who had mucormycosis and aspergillosis separately.[3,4,6–8,15,20,21,23,33,37,36,39,41,44,52,56,57,68,84,86,89,99,101,105,122,141,144,145,148–158] Table 22 summarizes comprehensive evidence surrounding systemic antifungal therapy for AIFS.

The three main classes of antifungal agents for the treatment of invasive fungal disease are polyenes, triazoles, and echinocandins. The most important polyene in routine use is amphotericin B. This is available as amphotericin B deoxycholate or as lipid-based formulations of amphotericin B and can be administered as intravenous therapy or topical therapy. The main side effect of amphotericin B is nephrotoxicity, which can be substantially reduced with use of lipid-based formulations,[167] and potentially further with adequate hydration.[168,169] Other side effects include electrolyte disturbances[21] and infusion-related reactions.[32] Triazoles include voriconazole, posaconazole, and isavuconazole. These are available as both IV and oral therapies. The main side effect of triazoles is hepatotoxicity,[170] and thus monitoring of hepatic enzymes is important. Other side effects specific to voriconazole include vision changes, neurologic toxicity, skin toxicity, and cardiac toxicity.[171] Echocandins include micafungin, caspofungin, and anidulafungin. These are typically administered IV. Adverse events are generally mild, including local phlebitis and abnormal liver function tests.[172]

10.2 | Empiric therapy

Once suspicion of AIFS is high, empiric therapy with amphotericin B should be initiated promptly to shorten the delay in treatment.[39,99,156] This is primarily because of high mortality rates seen amongst AIFS patients.[5,23,24,45,51,63,122,125,173] A large study amongst patients with mucormycete infection of any variety (e.g., pulmonary) reported that a delay of more than 6 days before initiation of treatment resulted in a twofold increase in mortality at 12 weeks.[66]

The basis for use of amphotericin B as empiric therapy is based on expert recommendation[174] and first principles that amphotericin B has broad-spectrum coverage of both

TABLE 21 Evidence for return to operating room.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Malleshappa[21]	2020	3	Cohort study	51 patients with AIFS	1) Reoperation decision 2) Overall survival	Residual disease noted on weekly endoscopic debridement returned to OR for repeat debridement. No difference in survival between patients with 1 and >1 surgery ($p = 0.09$).
Kashkouli[147]	2019	3	Cohort study	63 patients with rhino-orbito-cerebral mucormycosis	Overall survival	No difference in survival between those who received 1 or 2 vs. 3 surgeries.
Silveira[63]	2019	3	Cohort study	46 patients with AIFS; postoperative endoscopy every 24–48 hours was used to assess for signs of recurrence until neutropenia was recovered and signs/symptoms of disease resolved	Overall survival	With endoscopy every 24–48 hours after initial surgery, 14 patients were identified for repeat surgery. There was no significant difference in number of surgeries performed between those who survived and died.
Wu[146]	2018	3	Cohort study	21 diabetic patients with AIFS	Overall survival	No information on decision leading to OR return, but patients with multiple surgeries had improved survival.
Kolekar[143]	2015	3	Cohort study	20 patients with rhino-cerebral mucormycosis	Overall survival	Twice-weekly nasal endoscopy was used to identify recurrence, which was found in 20% of cases.
Yakirevitch[145]	2015	3	Cohort study	13 pediatric patients with AIFS	Overall survival	Nasal endoscopy every 3 days assessed recurrence initially, with follow-up endoscopy and imaging every 2 and 6 months, respectively, to further assess recurrence. Ten of 13 patients had recurrence, with 6 having died by the end of the study.
Vironneau[142]	2014	3	Cohort study	22 patients with rhino-orbito-cerebral mucormycosis with and without local control	Requirement for OR return and overall survival	Persistence of infection of histologic examination of surgical specimen and repeat endoscopy findings triggered repeat procedures. Local control occurred in 75% of survivors (45% of patients required reoperation) and 0% of patients who died.

(Continues)

TABLE 21 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Tarkan[148]	2012	3	Cohort study	13 pediatric patients hematology–oncology patients with AIFS	Reoperation decision	Reoperation in 8 patients guided by infection parameters (white blood cell count, procalcitonin, peripheral blood smears, C-reactive protein) and endoscopic and radiologic evaluation. Age, gender, underlying disease, and fungus subspecies did not predict OR return. No significant difference in survival in those with 1 surgery and >1 surgery
Saedi[125]	2011	3	Cohort study	30 patients with rhino-cerebral mucormycosis	Recurrence	Recurrence was detected on endoscopy in 10 patients, which led to OR return
Shanbag[33]	2019	4	Case series	8 patients treated for AIFS	Predictors of OR return	Serial diagnostic endoscopy guided OR return (>50% of patients required repeat surgery)
Ergun[36]	2017	4	Case series	19 patients with AIFS	Reoperation decision	Suspicious findings on postoperative endoscopy led to OR return in 6 patients. POf the patients requiring reoperation 33% survived.
Vinh[149]	2017	4	Case series	17 pediatric patients with AIFS	Overall survival	No difference in survival in patients who returned to OR <5 days and >5 days after prior surgery.
Valera[144]	2011	4	Case series	32 patients with AIFS	Overall survival	Periodic endoscopy and subsequent CT (with suspicious endoscopic findings) helped guide OR return decision.

TABLE 22 Systemic antifungal therapy.

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Comparison of liposomal amphotericin vs. other antifungals						
Turner[4]	2013	2	Systematic review of case retrospective series	807 AIFS patients; no data on percent *Mucor* vs. *Aspergillus* 77.5% amphotericin B, 15% liposomal amphotericin B, 5.4% voriconazole or posaconazole	Overall survival	Overall mortality was 50.3%. When comparing liposomal amphotericin vs. other antifungals, there was a significant difference in survival on univariate analysis, but it did not reach significance on multivariate analysis.
Raizada[8]	2018	4	Retrospective case series	22 AIFS patients with underlying diabetes 1 of 22 *Aspergillus*, and 22 of 22 *Mucor* All 22 patients received amphotericin B (13 conventional, 6 liposomal, 3 mix of both) and then stepped down to either posaconazole or voriconazole	Overall survival	Overall mortality 36% (8 of 22). Survival was similar among patients treated with liposomal and conventional amphotericin B ($p = 0.99$).
Roxbury[6]	2017	4	Retrospective case series	54 AIFS patients; 27% *Aspergillus* 27.8% *Mucor* 37 patients received amphotericin B–based therapy, whereas 13 received non-amphotericin B–based therapy	Overall survival	Mortality was 39.8%. No difference was seen in mortality with amphotericin B–based vs. non-amphotericin B–based medical therapy ($p = 0.4$). Authors commented that there is no standard antifungal regimen used. Antifungal agents could not be compared due to tendency to treat with multidrug therapy.
Amphotericin monotherapy						
Gillespie[159]	2000	3	Prospective nonrandomized trial to assess the role of middle turbinate biopsy	8 AIFS patients; 6 *Aspergillus*, 1 *Mucor* All patients were treated with high-dose amphotericin B	Overall survival	Mortality was 63%.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Tarkan[148]	2012	3	Cohort study	13 pediatric hematology/oncology AIFS patients 5 of 13 *Mucor*, 8 of 15 *Aspergillus* All patients treated with amphotericin B	Overall survival	Mortality was 53% (7 of 13). Authors concluded AIFS requires prompt medical and surgical therapy.
Saedi[125]	2011	3	Retrospective case series	30 patients with endoscopically treated rhinocerebral mucormycosis All patients were treated with IV and topical amphotericin B	Overall survival	Overall survival was 60%. Authors concluded a combination of endoscopic surgical debridement plus topical amphotericin B use, followed by IV amphotericin B therapy, is acceptable in the management of selected patients, and has less morbidity compared with conventional treatment.
Bhansali[45]	2004	3	Cohort study	35 patients with rhino-orbital-cerebral mucormycosis and diabetes All patients were treated with amphotericin B	Overall survival	Overall survival was 21 of 35 (60%). Authors concluded amphotericin B is partially effective, so surgical debridement is essential.
Piromchai[122]	2014	4	Retrospective case series	45 patients with AIFS No description of percentage of mucomycosis vs. *Aspergillus* All patients were treated with standard debridement and IV amphotericin	Overall survival	Overall survival was 58.9%. Authors concluded appropriate treatment should be administered within 14 days from onset of symptoms.
Toumi[160]	2012	4	Retrospective case series	5 patients with rhino-cerebral mucormycosis All patients were treated with amphotericin B	Overall survival	Mortality was 60% (3 of 5). Authors suggested curative treatment is medical and surgical. Standard antifungal therapy should be IV amphotericin B for 10–12 weeks. Careful surveillance of renal function is important. Posaconazole was suggested as a second-line drug for amphotericin B treatment failure.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Suslu[44]	2008	4	Retrospective case series	19 patients with AIFS; 9 *Mucor*, 6 *Aspergillus* All patients were treated with amphotericin B	Overall survival	Mortality was 68.5% (13 of 19). Authors recommended antifungal therapy—most commonly amphotericin B, but also noted that new drugs, including caspofungin, voriconazole, ravuconazole, and liposomal amphotericin B, have been used. They also recommended administration of amphotericin B before exact histopathologic diagnosis is made.
Hosseini[161]	2005	4	Retrospective case series	10 patients with rhinocerebral mucormycosis All patients treated with IV amphotericin	Overall survival	Overall survival 60%.
Rizk[150]	2000	4	Retrospective case series	7 AIFS patients undergoing chemotherapy for underlying malignancy; 6 *Aspergillus*, 1 *Candida* All patients were treated with IV amphotericin B	Overall survival	Mortality was 28.5% (2 of 7). Authors concluded most important factor for treatment success is recovery of patient's immune system.
Sohail[47]	2000	4	Retrospective case series	9 AIFS patients; *Mucor* was identified on culture for all cases All patients were treated with amphotericin B–based therapy	Overall survival	Thirty-three percent mortality rate. Authors concluded that treatment involves surgical debridement, amphotericin B, and management of underlying medical problems.
Drakos[52]	1993	4	Retrospective case series	11 bone marrow transplant patients who developed AIFS: 8 *Aspergillus*, 1 *Mucor*, 1 *Candida*, and 1 *Fusarium* All patients were treated with amphotericin B–based therapy	Overall survival	Mortality was 82% (9 of 11). Authors concluded that early diagnosis, aggressive multidisciplinary therapy, including systemic treatment with new preparations of amphotericin B, particularly amphotericin B colloid dispersion in conjunction with granulocyte transfusions, may improve outcomes.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Peterson[162]	1989	4	Retrospective case series	21 patients with neutropenia from cancer treatment who developed *Aspergillus* AIFS All patients received amphotericin B	Overall survival	Mortality was 21% (4 of 21). Authors recommended empiric treatment if risk factors favoring a diagnosis of *Aspergillus* are present. Liposomal encapsulation of amphotericin B may reduce drug toxicity and enhance efficacy.
Azoles						
Durand[158]	2021	3	Post-hoc analysis of control arm of randomized trial	50 AIFS patients; 21 *Aspergillus*, 17 *Mucor* All patients received isavuconazole	1) Overall survival 2) Clinical success of treatment	Mortality was 18% at day 42 and 30% at day 84. Sixty percent had clinical success (18 complete, 9 partial). Authors concluded findings should be interpreted with caution in view of the study's retrospective nature and inclusion of data from 2 trials.
Manesh[163]	2016	4	Retrospective case series	12 patients with rhino-orbital-cerebral mucormycosis All patients treated with posaconazole (6 due to renal toxicity with amphotericin, 3 due to residual disease after amphotericin B)	1) Clearance of disease 2) Overall survival	Complete clearance of disease in 66.6% of patients was achieved. Mortality was 0% (median follow-up 9 months). Authors concluded their results show a promising role for posaconazole and suggest its use as the primary antifungal agent of choice after an initial short course of polyene therapy.
Comparison of amphotericin B vs. voriconazole						
Fernandez[23]	2017	3	Cohort study	19 AIFS patients; 26.3% *Mucor*, 52.6% *Aspergillus*; first-line antifungal treatment was amphotericin for 13 of 18 patients and voriconazole for 1 patient	Overall survival	Overall mortality was 68.4% at 24 months. No statistical difference was seen in outcomes when amphotericin B was compared with voriconazole as first-line treatment $p = 0.78$.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Cho[39]	2015	4	Retrospective case series	45 AIFS patients; 30 *Aspergillus*, 14 *Mucor*, 1 *Aspergillus* + *Mucor*, 1 *Schizophyllum commune* 42 (93%) patients received amphotericin, 17 (38%) received voriconazole, and 2 received other antifungal agents	Overall survival	Mortality was 47% (21 of 45). No difference in overall survival was seen when comparing patients treated with amphotericin vs. voriconazole. Authors stated that early diagnosis is crucial for successful treatment and allows for empiric treatment using an antifungal agent.
Monroe[41]	2013	4	Retrospective case series	29 patients with AIFS treated surgically; 10 (34%) *Aspergillus*, 18 (62%) *Mucor* Patients were treated by infectious disease specialists with amphotericin B and/or voriconazole	Overall survival	Overall mortality was 79% (21 of 29). Treatment with amphotericin was found to show a trend toward increase in AIFS-attributable death ($p = 0.06$). Authors comment this could be related to its use more commonly in mucormycosis. However, when restricted to *Aspergillus* AIFS, a similar trend was noted ($p = 0.16$).
Comparison of monotherapy vs. combination therapy						
Candoni[3]	2019	3	Multicenter series	89 AIFS patients with hematologic malignancy; 22% *Mucor*, 70% *Aspergillus* Of the 61 *Aspergillus* patients, 37 were treated with amphotericin B and 27 with voriconazole Combination therapy was administered only in 1 patient; of the 20 *Mucor* cases, 9 received amphotericin B, 8 received amphotericin B with posaconazole, 1 received amphotericin B with caspofungin, and 1 received posaconazole alone	Overall survival	Overall mortality at 12 months was 69% (61 of 89). Combination antifungal therapy was not found to have a significant benefit in overall survival ($p = 0.614$).

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Vengerovich[56]	2020	4	Retrospective case series	34 AIFS patients; 44% *Mucor*, 38.2% *Aspergillus* 78.8% received amphotericin B alone or as a combination 42.4% received double-drug therapy, whereas 30.3% received triple therapy	Overall survival	Overall mortality was 61.8%. Single vs. double vs. triple antifungal agents were compared but no significant survival difference was seen. Authors commented that consensus guidelines are needed for for medical management. Amphotericin remains the mainstay agent, except for voriconazole for *Aspergillus*. Posaconazole is often used as second line.
Vinh[149]	2017	4	Retrospective case series	18 pediatric AIFS patients; 22.2% *Mucor*, 11.1% *Aspergillus* Most patients (16 of 17) were treated with combination antifungal therapy; 17 patients treated with amphotericin B 16 of 17 patients treated with an azole; 8 treated with an echinocandin	Overall survival	Overall mortality rate was 41% at 30 days and 59% at 6 months. Treatment with an echinocandin in addition to azole and amphotericin B did not correlate with a difference in overall survival. Authors concluded that echinocandin should remain as salvage therapy if primary antifungals (voriconazole, amphotericin B) cannot be used.
Foshee[105]	2016	4	Retrospective case series	27 AIFS patients; 78% *Mucor*, 17% *Aspergillus* 16 patients received amphotericin B alone, whereas 9 patients received amphotericin B + triazole and 2 patients received triazole alone	Overall survival	Mortality was 57.7%, with 23.1% dying from AIFS and 11% from complications of therapy. Mortality between the 3 medical regimens was similar ($p = 0.99$). Authors remarked that 4 patients in this series had new-onset organ failure and all 4 received amphotericin B. They urged caution and close monitoring in patients receiving amphotericin B.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Gode[84]	2015	4	Retrospective case series	34 AIFS patients who underwent surgery 19 (51.4%) *Mucor* 18 (48.6%) *Aspergillus* All patients received an amphotericin B regimen, whereas 9 patients also received voriconazole or posaconazole	Overall survival	Mortality was 64.9% (24 of 37). Authors remarked that, although amphotericin B is the main drug given for AIFS, combination with caspofungin, voriconazole, or posaconazole did show a statistically significant improvement in prognosis ($p > 0.05$).
Chen[68]	2011	4	Retrospective case series	46 AIFS patients with hematologic malignancy; 17 *Aspergillus*, 4 mucormycosis 28 patients received amphotericin B–based therapy, 2 voriconazole, 4 ampohotericin B + caspofungin, and 9 amphotericin B + voriconazole	Overall survival	Overall mortality 41% (19 of 27). Six-week survival was not significantly different between those who received antifungal combination therapy vs. those who received amphotericin alone ($p = 0.074$).
Combination therapy						
Argueta[157]	2019	4	Retrospective case series	18 AIFS pediatric patients; 13 of 18 *Aspergillus*, 1 *Mucor* All patients were treated with combination therapy with amphotericin and triazole with or without an echinocandin	Overall survival	Overall mortality was 75% (12 of 18); 89% of patients recovered completely from fungal sinusitis, whereas 2 patients were discharged and referred to palliative care for poor prognosis of underlying disease. Authors remarked that their series contained mainly patients with *Aspergillus* and thus voriconazole was used. Combination of antifungals may be more effective than monotherapy.
El Naaj[137]	2013	4	Retrospective case series	6 patients with rhinocerebral mucormycosis All patients were treated with amphotericin B and posaconazole/voriconazole	Overall survival	Mortality was 83.3% (5 of 6). Controlling the underlying disease with early diagnosis and aggressive surgical intervention appears to be the most important factor in survival

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Others—mix of various treatment regimens						
Malleshappa[21]	2020	3	Cohort study	51 AIFS patients; 31% *Mucor*, 19% *Aspergillus* All patients received amphotericin B Posaconazole was administered as salvage for 12 patients orally for 6 months; voriconazole was administered to *Aspergillus* patients	1) Overall survival 2) Disease-specific survival	Of the patients, 13.6% died from AIFS and 22.7% died of other causes
Yakirevitch[145]	2015	3	Cohort study	13 pediatric patients with AIFS treated surgically; 4 *Aspergillus*, 5 *Mucor* All *Mucor* patients were treated with amphotericin B or combination of amphotericin B and a triazole; the remaining patients were treated with voriconazole	Overall survival	Mortality was 54% (7 of 13).
Alejandro[20]	2020	3	Cohort study	18 pediatric AIFS patients: 14 *Aspergillus*, 3 *Mucor*, 1 *Fusarium* 6 patients received voriconazole; 10 patients received combination amphotericin and voriconazole, whereas 2 patients received combination amphotericin and posaconazole	Overall survival	Overall mortality was 33% at 6 months. Type of antifungal therapy did not have any impact on survival. Authors commented that amphotericin B remains the first-line treatment.
El-Kholy[153]	2021	4	Retrospective case series	36 patients with post–COVID-19 AIFS; 77% *Mucor*, 30.6% *Aspergillus* Liposomal amphotericin was given to 26 patients, voriconazole to 8 patients, and a combination of both in 2 patients; in 3 patients, voriconazole was replaced by posaconazole	Overall survival	Overall survival was 63.89%. Authors concluded that early recognition and rapid initiation of antifungal therapy with immediate surgical intervention could affect prognosis.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Huang[154]	2021	4	Retrospective case series	22 AIFS patients: 9 *Mucor*, 12 *Aspergillus*, 1 *Fusarium* 80% of patients received amphotericin B–based therapy; some patients shifted to posaconazole; 4 patients with cultured *Aspergillus* were treated with voriconazole	Overall survival	Ten of 22 survived.
Nam[101]	2020	4	Retrospective case series	50 patients with AIFS; 33 *Mucor*, 16 aspergillosis, 23 mucormycosis Patients were treated with IV amphotericin-based therapy, whereas 16 patients with aspergillosis were treated with IV voriconazole	1) Overall survival 2) Disease-specific survival	Seventy-four percent of patients were cured of AIFS, 12% had no remnant disease but died of other reasons, and 14% died of disease progression.
Shanbag[33]	2019	4	Retrospective case series	8 AIFS patients; 6 of 8 *Mucor*, 2 of 8 *Aspergillus* All patients were treated with liposomal amphotericin B; in cases with contradictory results of KOH mount or insufficient response, azole drugs were started	Overall survival	Mortality was 0%. Authors suggested liposomal amphotericin as first line with posaconazole as salvage. Other options, such as capsofungin, have been used but have limited data and high cost.
Hirabayashi[57]	2019	4	Retrospective case series	55 AIFS patients; 27 ascomycota, 21 mucormycota 75% of patients received combination antifungals, 76% received amphotericin, 64% caspofungin, 42% voriconazole, and 27% posaconazole	Overall survival	Mortality was 45%.
Abdollahi[26]	2017	4	Retrospective case series	15 patients with rhino-orbital-cerebral mucormycosis 12 of 15 treated with amphotericin B	Overall survival	Twelve of 15 survived. Authors concluded medical therapy alone is ineffective due to poor drug delivery and thus surgical treatment is essential for successful eradication of disease

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Green[15]	2016	4	Retrospective case series	14 pediatric AIFS patients; 5 *Aspergillus*, 7 *Mucor*, 2 *Alternaria*, 1 scopulariopsis All patients received prolonged culture-based antifungal therapy, including amphotericin B, voriconazole, posaconazole, caspofungin and micafungin	1) Overall survival 2) AIFS-related survival	AIFS-related mortality rate was 2 of 14 (14.3%), whereas overall mortality was 4 of 14 (28.6%).
Pagella[156]	2016	4	Retrospective case series	10 AIFS patients with underlying hematologic malignancy; 8 *Aspergillus*, 1 *Mucor*, 1 both *Mucor* and *Fusarium* All patients received liposomal amphotericin B and voriconazole (although some cases had itraconazole or posaconazole after *Aspergillus* was identified)	Overall survival	Mortality was 40% (4 of 10). Authors remarked that amphotericin B is still the drug of choice in most places but could often be replaced by liposomal formulations. Other antifungal drugs that should be considered are itraconazole, posaconazole, voriconazole, and echinocandines.
Bakhshaee[37]	2016	4	Retrospective case series	18 AIFS patients; 27.8% *Aspergillus*, 72.23% *Mucor* 15 patients were treated with amphotericin B, whereas 3 were treated with voriconazole/posaconazole	Overall survival	Mortality was 20% (3 of 15).
Ergun[36]	2017	4	Retrospective case series	19 AIFS patients; 9 *Mucor*, 9 *Aspergillus* 19 patients received IV liposomal amphotericin B, which was switched to long-term oral voriconazole or itraconazole after discharge. If *Aspergillus* was histopathologically proven, IV liposomal amphotericin B was switched to IV voriconazole.	Overall survival	Mortality was 61.2%. Authors commented that liposomal amphotericin B is preferred over liposomal amphotericin B.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Trief[155]	2015	4	Retrospective case series	24 AIFS patients; 14 *Mucor*, 7 *Aspergillus* 20 of 24 patients received amphotericin; in patients with *Aspergillus* diagnosis, amphotericin was switched to voriconazole	Overall survival	Mortality was 54.2% (13 of 24). Authors stated that all patients with mucormycosis were treated with liposomal amphotericin B. Liposomal amphotericin appears to be superior. Authors recommend that, if there is suspicion of AIFS, empiric systemic amphotericin be administered with consultation with infectious disease specialists.
Davoudi[7]	2015	4	Retrospective case series	44 patients with hematologic malignancies who developed AIFS; 13 *Mucor*, 9 *Aspergillus*, 9 *Fusarium* 9 patients received monotherapy with lipid-based amphotericin B, echinocandin, or triazole; 26 patients received 2 drug combinations (liposomal amphotericin B + echinocandin/triazole *OR* echinocandin + triazole); 9 patients received triple therapy	1) Overall survival 2) Disease-specific survival	Overall mortality was 36.4% at 6 weeks and 45.5% at 12 weeks. Antifungal therapy with a triazole-containing regimen was associated with a decreased 6-week all-cause ($p = 0.032$; HR, 0.33) and IMS-attributable ($p = 0.038$; HR, 0.31) mortality. Authors remarked treatment with azole-containing regimens were shown as a positive predictor factor in this study, perhaps because of the predominance of AIFS cases due to non-*Mucor* fungi where voriconazole had activity.
Kim[99]	2015	4	Retrospective case series	21 patients with AIFS; 16 (51.6%) *Mucor*, 2 (6.5%) *Aspergillus* 14 patients received amphotericin B alone, 3 patients received amphotericin B and micafungin and/or posaconazole, 1 patient received amphotericin B and subsequent caspofungin and voriconazole; 2 patients with aspergillosis and 1 patient with unknown species was treated with voriconazole and/or subsequent posaconazole or caspofungin	Overall survival	Mortality was 23.8% (5 of 21). Authors mentioned that most patients received empiric antifungal therapy, which is a critical factor in survival.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Ardeshirpour[141]	2014	4	Retrospective case series	11 pediatric patients with hematologic malignancy diagnosed with AIFS, including 4 *Aspergillus* and 7 *Alternaria* All patients received amphotericin B; 10 of 11 received azole therapy with voriconazole or itraconazole, and 3 also received caspofungin	Overall survival	Mortality rate 27% (3 of 11). Authors concluded that timely aggressive surgical treatment combined with antifungal and supportive therapy can lead to successful eradication of infection.
Valera[144]	2011	4	Retrospective case series	32 AIFS cases in immunocompromised patients, with 13 *Aspergillus*, 11 *Mucor*, and 2 *Fusarium* Amphotericin used as monotherapy in 21 patients and in association with other antifungal drugs in 6 patients In cases where *Aspergillus* was identified or if amphotericin could not be tolerated, voriconazole and fluconazole were used	Overall survival	Mortality was 50% (16 of 32). Authors indicated clinical and surgical treatment must be promptly initiated once AIFS is diagnosed. Amphotericin B was used most frequently, whereas voriconazole was considered treatment of choice once *Aspergillus* AIFS was diagnosed.
Hachem[164]	2008	4	Retrospective case series	39 patients with *Aspergillus* AIFS in neutropenic patients with cancer 18 patients received amphotericin B–based therapy 8 patients received polyene and itraconazole combined therapy, whereas 3 patients received polyene and echinocandin combined therapy	Overall response	Overall response was 12 of 39 (31%). Authors recommended aggressive medical therapy should be started early to improve outcomes.
Reed[165]	2008	4	Retrospective case series	41 cases of rhino-orbital-cerebral mucormycosis. 7 patients received combination amphotericin B based therapy + caspofuingin while the rest were treated with amphotericin B–based therapy	1) Overall survival 2) Treatment success	Overall survival was 54% (considered survived if alive at 30 days after hospital discharge). Combination therapy shown to have an odds ratio of 9 (univariate, $p = 0.03$) and 10.9 (multivariate, $p = 0.02$) for success at 30 days after hospital discharge.

(Continues)

TABLE 22 (Continued)

Study (first author)	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Roongrotwattanasiri[151]	2007	4	Retrospective case series	5 patients with AIFS 1 had *Aspergillus*, no details for other 4 All 5 treated with IV amphotericin, with 1 patient treated with oral itraconazole	Overall survival	Four of 5 survived the treatment.
Vener[152]	2007	4	Retrospective case series	5 AIFS patients with underlying hematologic malignancy All 5 patients had *Aspergillus*, whereas 2 also had *Mucoracea* and *Fusarium* 4 of 5 patients treated with amphotericin B; 1 patient switched to IV echinocandin + voriconazole	Overall survival	Mortality was 40%.
Park[86]	2005	4	Retrospective case series	9 pediatric AIFS patients with hematologic/lymphoid neoplasms 2 *Aspergillus*, 4 *Fusarium*, and 2 *Alternatia* All patients were treated with 2 or 3 agents, including lipid preparations of amphotericin B, caspofungin, itraconazole, voriconazole, or posaconazole	Disease-specific survival	Two of 9 (22%) died of fungal infection. Authors concluded that, with the wide range of organisms causing AIFS and the availability of new classes of antifungal agents, growing the specific organism is vital. This would allow aggressive antifungal therapy tailored based on identification and susceptibility of the organism.
Siddiqui[166]	2004	4	Retrospective case series	25 immunocompetent patients with craniocerebral aspergillosis of sinonasal origin All patients with cerebral involvement received IV amphotericin B followed by orally administered itraconazole in divided doses for 8–12 months Patients with only sinonasal involvement received itraconazole alone for a prolonged period.	Overall survival	Seven of 25 patients died (28% mortality). Authors concluded response to antifungal triazoles may sometimes be superior to that achieved with IV amphotericin B.
Iwen[49]	1997	4	Retrospective case series	17 AIFS patients, with 12 *Aspergillus*, 1 *Alternia*, and 1 *Rhizopus* All patients treated with amphotericin B, with some patients also treated with flucytosine, fluconazole, ketoconazole, and itraconazole	Overall survival	Mortality was 52% (9 of 17).

Mucorales and aspergillosis. On the other hand, *Mucorales* have innate resistance to some azoles, which are a first-line therapy for aspergillosis.[175] There were seven series, which reported use of empiric antifungal therapy before confirmation of fungal species. Three studies reported use of amphotericin B,[36,52,152] whereas the other four either used a variety of antifungals[68] or did not give further details on which antifungal agent was used.[7,99,101] When amphotericin B is used, liposomal amphotericin B is recommended in view of the increased risk of renal injury with other formulations.[167] Although empiric antifungal therapy may be considered if suspicion of AIFS is adequately high, it is ultimately up to the involved surgeons to obtain a tissue sample to confirm the diagnosis of AIFS, if considered indicated. Once an organism is identified, targeted antifungal therapy can then be employed. Table 23 summarizes evidence surrounding empiric antifungal therapy for AIFS.

Aggregate Grade of Evidence	C (Level 4: 7 studies)
Benefit	Delay in treatment appears to have a significant impact on survival and thus empiric antifungals are suggested to improve overall survival.
Harm	Risks associated with use of empiric antifungals include additional toxicity associated with early initiation of antifungals (renal toxicity, hepatotoxicity, electrolyte disturbances, and infusion-related reactions).
Cost	Cost of antifungals must be weighed with costs of delayed treatment and its impact on prognosis.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	There is a paucity of evidence investigating the use of empiric antifungals and their impact on survival outcomes. In view of the aggressive nature of disease and the impact of delay in treatment, many studies recommend use of empiric antifungal therapy.
Policy Level	Option: Option to start empiric antifungals based on clinical suspicion and in the setting of relevant medical comorbidities. The overall evidence to suggest efficacy of empiric antifungals in IFS is low as data were abstracted from studies in pulmonology.
Aggregate Grade of Evidence	**C (Level 4: 7 studies)**
Intervention	Empiric antifungals are an option for patients with high clinical suspicion for IFS, especially in those with relevant medical comorbidities. Lipid-based amphotericin B is recommended in view of susceptibility of both mucormycosis and *Aspergillus* AIFS and decreased toxicity associated with lipid formulations.

10.3 | Systemic antifungals for aspergillosis

Aspergillus spp. are common causative organisms in AIFS. Voriconazole has traditionally been recommended as the first-line therapy. This is borne out of a randomized controlled trial including 277 patients treated for invasive aspergillosis; a successful outcome was seen in 52.8% of patients in the voriconazole group, but in only 31% of patients in the amphotericin B deoxycholate group.[67] However, this cohort only included 25 patients with sinus or cerebral invasive aspergillosis. Among AIFS patients specifically, there were only two case series that compared amphotericin and voriconazole, and both had a mix of mucormycosis and aspergillosis patients.[39,41] In a study by Monroe et al., a subgroup analysis of aspergillosis patients was performed and there was a trend toward improved mortality among patients undergoing voriconazole treatment, but it did not reach statistical significance.[41] Most other *Aspergillus* AIFS series reported a variety of antifungal treatment. Among AIFS patients in general, there were many series that reported use of voriconazole.[20,21,101,145,154,155] Voriconazole is typically administered IV initially and then stepped down to oral therapy depending on clinical, biochemical, and radiologic features.

Isavuconazole and posaconazole have also been identified as alternatives for invasive *Aspergillus* infections. Two randomized controlled trials were performed among patients with invasive aspergillosis of any variety, and not specifically among patients with AIFS. The two trials showed similar outcomes with a potentially improved side-effect profile when compared with voriconazole.[176,177] Among AIFS patients, Durand et al. reported a 60% clinical success rate and 70% overall survival with use of isavuconazole alone, although this cohort had a mix of mucormycosis (34%) and *Aspergillus* (42%) patients.[158] Posaconazole was used in a number of AIFS series not specific to *Aspergillus*.[154,156]

TABLE 23 Empiric antifungal therapy.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Nam[101]	2020	4	Retrospective case series	50 patients with AIFS 34 (68%) patients underwent preoperative empiric antifungal medication (not specified which type)	1) Overall survival 2) Disease-specific survival	Seventy-four percent of patients were cured of AIFS; 12% had no remnant disease, but died of other causes; 14% died of disease progression. Preemptive antifungal treatment was not shown to have any significant impact on disease-specific survival ($p = 0.605$).
Ergun[36]	2017	4	Retrospective case series	19 AIFS patients If a strong suspicion for AIFS was present, then IV liposomal amphotericin B therapy was initiated empirically	Overall survival	Mortality was 61.2%. Authors commented that liposomal amphotericin B is preferred over liposomal amphotericin B.
Kim[99]	2015	4	Retrospective case series	21 patients with AIFS Empirical antifungal therapy was initiated in 17 of 21 patients (not mentioned what was administered)	Overall survival	Mortality was 23.8% (5 of 21). Empirical antifungal therapy (received <6 days after the onset of symptoms of AIFS) was initiated in 12 of 16 survivors (75.0%) and all 5 nonsurvivors (100.0%).
Davoudi[7]	2015	4	Retrospective case series	44 patients with hematologic malignancies who developed AIFS 23 patients (52.3%) received preemptive antifungal treatment	1) Overall survival 2) AIFS-associated survival	Overall mortality 36.4% at 6 weeks and 45.5% at 12 weeks.
Chen[68]	2011	4	Retrospective case series	46 AIFS patients with hematologic malignancy Preemptive antifungal treatment given in 43 of 46 patients (94%) with AIFS 28 amphotericin B, 2 voriconazole, 9 combination amphotericin and caspofungin/voriconazole	Overall survival	Overall mortality 41% (19 of 27). No difference in overall survival when various preemptive antifungal agents were compared ($p = 0.29$).
Vener[152]	2007	4	Retrospective case series	5 AIFS patients with underlying hematologic malignancy All 5 patients were initiated on empiric amphotericin B	Overall survival	Mortality 40%.
Drakos[52]	1993	4	Retrospective case series	11 bone marrow transplant patients who developed AIFS 4 of 11 patients treated with amphotericin B empirically	Overall survival	Mortality was 82% (9 of 11).

Whenever azole resistance is seen, liposomal amphotericin B remains an alternative monotherapy as well. A prospective study showed response rates of about 50% with use of liposomal amphotericin B among patients with invasive aspergillosis of all varieties.[178] Among patients with AIFS, there were two retrospective case series and one systematic review analyzing liposomal amphotericin B.[4,8,23] Liposomal amphotericin B was shown to provide a significant improvement in survival compared with other antifungals in a systematic review by Turner et al.[4]; however, this did not reach significance in the multivariate analysis.

Echinocandins have not been well studied among AIFS patients but may be considered as part of combination therapy strategies. A recent systematic review analyzing caspofungin in invasive aspergillosis identified low levels of evidence, suggesting it may likely be safe and efficacious, but concluded that additional prospective studies are needed.[179]

Combination antifungal therapy is not routinely recommended but can be considered as salvage therapy in very severe cases of *Aspergillus* AIFS. In a randomized controlled trial of combination therapy of voriconazole plus anidulafungin vs. voriconazole alone in invasive aspergillosis, there was a suggestion of improved outcomes among patients with combined therapy.[180] Among AIFS patients, there have been six case series making this comparison and they showed no difference in survival.[3,56,68,84,105,149] Combination antifungal therapy with triazole and echinocandin as well as liposomal amphotericin and echinocandin have been used, but triazole and liposomal amphotericin are often favored for central nervous system infections.[181,182]

10.4 | Systemic antifungals for mucorales

Unlike in aspergillosis, the *Mucorales* order of organisms has shown innate resistance to voriconazole,[27] and thus a recently published guideline recommended liposomal amphotericin B as first-line therapy.[183] Should central nervous system (CNS) involvement be seen, the dose delivered can be increased up to 10 mg/kg. Although most mucormycosis AIFS series reported use of amphotericin B,[26,45,47,125,137,161,160] there are only three publications that compared amphotericin B to other antifungals. Two retrospective case series compared and showed no difference in survival, whereas one large systematic review showed a significant difference in survival in the univariate analysis when comparing liposomal amphotericin with other antifungals.[4,8,23] These series did not separate *Aspergillus* from mucormycosis.

For patients who are intolerant or refractory to liposomal amphotericin, isavuconazole and posaconazole are both potential options due to their activity against *Mucorales*. Although both drugs have been shown to be effective as salvage therapy among patients with mucormycosis of all varieties,[184,185] only isavuconazole has been shown, in a small number of patients in the Isavuconazole in the Treatment of Renally Impaired Aspergillosis and Rare Fungi (VITAL) study, to be effective as primary treatment for mucormycosis of all varieties.[185] Manesh et al. reported a series of 12 AIFS patients with mucormycosis who received posaconazole—66.6% achieved complete clearance of disease with a 0% mortality rate (median follow-up of 9 months).[163]

There is significant debate over the benefit of combination therapy in the initial treatment of mucormycosis. A small, retrospective study in 2008 showed a survival benefit for combination therapy with amphotericin and an echinocandin compared with amphotericin alone, although the number of patients in the combination group was small.[165] However, this was not borne out in other larger retrospective series among AIFS patients in general (including patients infected with both *Mucor* spp. and *Aspergillus* spp).[68,84,149] There is also interest in using an azole with activity against mucormycosis (posaconazole or isavuconazole) in combination with amphotericin. The benefit of such a strategy remains unclear, as a number of studies in AIFS patients of mixed etiology showed no significant differences in survival with polyene given in combination with triazoles.[68,84,105] One benefit of early combination therapy with an azole is that, if patients are intolerant of liposomal amphotericin, it can be held or stopped and the patient will still be on active therapy, without needing to wait several days to reach steady-state levels if an azole was only started at that point.

Induction therapy with liposomal amphotericin is usually continued for at least 3 weeks before stepping down to an oral azole.[186] Oral azole therapy is then continued for a prolonged duration of therapy, at least 3 to 6 months[184,185] and often much longer, depending on the immune status of the patient (e.g., if immunosuppression is reversible). The decision as to which azole for stepdown therapy should be made on an individual basis, taking into consideration the side-effect profile of the drugs (e.g., isavuconazole does not prolong the QT interval), the need to monitor levels (e.g., there is more data and clinical experience for therapeutic drug monitoring with posaconazole), fungal minimal inhibitory concentrations if available (although these are not clearly associated with outcomes), and whether or not there is concern for development of breakthrough invasive fungal infections while on long-term azole therapy. This latter point is notable because isavuconazole has recently

been linked to breakthrough fungal infections, especially in patients who are solid-organ transplant or hematologic malignancy patients.[187,188]

10.5 | Systemic antifungals for atypical organisms

AIFS caused by rare or atypical fungal pathogens, such as *Fusarium*, *Scedosporium*, *Alternaria*, *Paecilomyces*, and *Scopularopsis* spp., should be treated in conjunction with an infectious diseases specialist and guided by existing expert consensus guidelines.[189] There were no AIFS case series focusing specifically on these atypical organisms, although some larger series included occasional patients with these atypical organisms.[7,20,52,86,144,152,154,156] There are several novel antifungal agents in different stages of development, such as orotamide olorofim and the glycosylphosphatidylinositol inhibitor fosmanogepix, which have activity against resistant and atypical organisms[190,191] and may be future options in the treatment of AIFS.

Aggregate Grade of Evidence	C (Level 3: 3 studies; Level 4: 50 studies)
Benefit	Almost all series in the literature reported use of antifungals in treatment of AIFS, except palliatively treated patients. Antifungals appear to improve survival compared with no antifungals, although no direct comparison was possible.
Harm	Risks associated with antifungals include potential renal toxicity, hepatotoxicity, electrolyte disturbances, and infusion-related reactions.
Cost	Cost of antifungals must be weighed with costs of entire hospitalization with and without antifungals.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	There is a paucity of evidence investigating the types of antifungals and their impact on survival outcomes. Most series report use of some form of antifungals.
Policy Level	Recommendation: Recommend use of antifungals in AIFS, although there are no conclusive data on specific antifungal medication.
Intervention	Antifungals should be initiated in all patients with AIFS. Type of antifungal employed should be decided in conjunction with infectious disease specialists, with consideration of the suspected fungal pathogens involved.

10.6 | Duration of therapy for AIFS

There is a paucity of evidence that has compared treatment duration for AIFS because endpoints are not standardized and practice patterns vary. At a minimum, therapy should be continued until all clinical and radiologic abnormalities have resolved with no microbiologic evidence of infection, and the involvement of an infectious disease specialist can help determine the duration of medical therapy. Factors such as disease extension (i.e., intraorbital, cavernous sinus, intracranial), smoking status, absence of a rhinologist on the treatment team, low absolute neutrophil count, hematologic malignancy, recent chemotherapy, and delayed time to surgery can be correlated with treatment duration.[52,44(p19),89,150] Although there are no definitive and consistent recommendations for duration of medical therapy, Table 24 demonstrates reported experiences with duration of systemic antifungal therapy in AIFS, mostly ranging from 3 weeks to 12 months, and summarizes evidence surrounding the duration of antifungal therapy for AIFS.

Aggregate Grade of Evidence	C (Level 3: 3 studies, Level 4: 18 studies, Level 5: 1 study)
Benefit	Appropriate duration of medical therapy will improve disease control and survival.
Harm	There are risks of potential adverse events with any duration or prolonged medical therapy, especially in patients with weak tolerance to such medications.
Cost	Overall cost of medical therapy should be considered, which includes the direct cost of medications and the indirect cost of hospitalization or management of adverse events.
Benefits–Harm assessment	Benefit likely outweighs costs and adverse risks for patients who meet candidacy and show good tolerance.
Value Judgments	There is a paucity of evidence investigating the exact duration of medical therapy for this rare disease. The duration of medical therapy depends on each patient's clinical presentation, and all will benefit from a multidisciplinary discussion.
Policy Level	No recommendation: No clear evidence for duration of medical therapy needed for AIFS as the data are currently limited.
Intervention	No clear consensus exists regarding the exact duration of medical therapy and thus no definitive evidence-based conclusions can be drawn with the existing literature.

TABLE 24 Duration of antifungal therapy.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Malleshappa[21]	2020	3	Cohort study	Patients with AIFS (n = 51)	Need for repeat surgery	Duration of amphotericin B therapy was determined by patients' ability to tolerate the drug without side effects and its affordability. After discharge, some patients were administered oral posaconazole for a period ranging from 3 to 9 months, depending on ability to continue the drug.
Alejandro[20]	2020	3	Cohort study	Pediatrics with AIFS ($n = 18$)	Survival	Of the 6 patients who received vericonazole systemic therapy, 1 was for <21 days and 5 were for >21 days; of the 10 patients who received amphotericin B/voriconazole therapy, 1 was for <21 days and 9 were for >21 days; of the 2 patients who received amphotericin B/posaconazole therapy, both were for >21 days. There were no significant differences between treatments of >21 vs. <21 days.
Wandell[5]	2018	3	Case–control study	AIFS ($n = 114$)	Survival	IV antifungal agent was given, on average, for 22 days, broken down into a mean 21 days for patients with hematologic malignancy, mean 21 days for patients with diabetic mellitus, and mean 13 days for patients with other diseases.
Gupta[192]	2009	4	Case–control study	Invasive *Aspergillus* sinusitis (n = 74)	Disease recurrence	Primary treatment included endoscopic clearance and oral itraconazole for 6 months; for treatment of recurrence, oral itraconazole was given for 6 months, and, for residual disease, surgery and oral itraconazole for 3 months showed the best survival.
Balai[193]	2020	4	Case series	Patients with acute rhinocerebral mucormycosis ($n = 9$)	Survival	First-line medical treatment consisted of IV amphotericin-based antifungals, with a course of at least 6 weeks usually required.
Adulkar[194]	2019	4	Case series	Invasive sino-orbital fungal infections in immunocompetent patients ($n = 20$)	Vision symptoms and orbital imaging	Medical therapy consisted of oral itraconazole in all patients and IV amphotericin B in 2 patients. Average duration of medical therapy required to achieve relief from symptoms was 6–8 months.
Abdollahi[26]	2017	4	Case series	Rhino-orbito-cerebral mucormycosis ($n = 15$)	Disease control and survival	Conventional amphotericin B treatment (average total dose of 50 mg/day) was administered for 5–31 days.

(Continues)

TABLE 24 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Baeesa[195]	2017	4	Case series	Invasive sinonasal aspergillosis with orbitocranial extension ($n = 12$)	Disease control	Alongside surgery, medical treatment consisted of IV amphotericin B for 2 weeks followed by oral itraconazole or voriconazole for 3–12 months. The length of treatment endpoint of oral therapy was complete radiologic clearance of the disease.
Manesh[163]	2016	4	Case series	Invasive rhino-orbito-cerebral mucormycosis ($n = 12$)	Disease control	In addition to surgery, all patients received oral posaconazole treatment for 2, 3 ($n = 3$), 4, 5, 6 ($n = 3$), 7, and 12 ($n = 2$) months.
Kennedy[196]	2016	4	Case series	Invasive mucormycosis ($n = 74$)	Survival	Antifungal treatment was initiated in 86% of patients and continued for a median of 64.5 (IQR, 21–365) days. Of those who survived 180 days ($n = 33$), the median treatment duration was 196 (IQR, 64–587) days.
Green[15]	2016	4	Case series	Pediatric AIFS ($n = 14$)	Survival	In conjunction with surgery, all patients received prolonged cultured-based antifungal therapy, including ambisome, voriconazole, posaconazole, caspofungin, and micafungin. Length of treatment varied greatly, ranging from 6 weeks to >2 years, and there was no statistical significance in outcomes based on length of treatment.
Sachdeva[197]	2013	4	Case series	Rhino-ocular cerebral mucormycosis with cranial nerve palsies ($n = 6$)	Survival	Amphotericin B was given IV for 6 weeks.
Toumi[160]	2012	4	Case series	Acute rhino-orbito-cerebral mucormycosis ($n = 5$)	Survival	Four patients were given IV amphotericin B for 8, 14, 26, and 49 days. One patient received IV amphotericin B for 60 days, followed by ketoconazole for 45 days.
Takahashi[43]	2011	4	Case series	AIFS ($n = 4$)	Survival	All patients received systemic antifungal agents (voriconazole and micafungin in 3 patients, and just micafungin in 1 patient) for 3 months.
Gallien[198]	2008	4	Case series	Invasive aspergillosis ($n = 34$)	Survival	All patients received antifungal therapy (amphotericin B, itraconazole, voriconazole, or a combination thereof), with a median duration of 63 days (range, 5–769 days).

(Continues)

TABLE 24 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ammari[199]	2008	4	Case series	Diabetic patients with AIFS ($n = 4$)	Survival	Two patients received amphotericin B: 1 for 98 days (alive at study conclusion) and the other for 6 days (died at day 6 from acute renal failure).
Vener[152]	2007	4	Case series	AIFS ($n = 5$)	Survival	Treatment varied from 77 to 365 days and depended primarily on the time to response, which was conditioned by factors such as the underlying immune status and extent of surgical debridement. The treatment was continued until radiologic and endoscopic evidence of complete remission.
Baumann[200]	2006	4	Case series	Invasive sphenoidal aspergillosis ($n = 4$)	Disease control	Two patients initially received amphotericin B (6 and 12 days), but this treatment had to be stopped because of acute renal toxicity. All patients were then treated with oral voriconazole for 12–14 weeks.
Siddiqui[166]	2004	4	Case series	Craniocerebral aspergillosis of sinonasal origin in immunocompetent patients ($n = 25$)	Survival	Mean duration of itraconazole therapy (whether alone or in combination) was 7.1 (range, 3–18) months for all patients. Similarly, in patients who survived during the study period ($n = 18$), the mean duration of itraconazole was 8 (range, 3–18) months, and only 1 patient who received itraconazole therapy for 12 months died.
Herbrecht[201]	2001	4	Case series	Invasive mucormycosis ($n = 21$)	Survival	Treatment involved amphotericin B colloidal dispersion. Patients were given a mean of 28 doses over a mean duration of 37 days; 9 patients did not receive daily therapy—those on maintenance therapy received it every other day or twice weekly, and therapy was temporarily stopped in patients with severe intercurrent conditions.
Drakos[52]	1993	4	Case series	AIFS in bone marrow transplant patients ($n = 11$)	Survival	All patients received systemic amphotericin B (7 conventional and 4 amphotericin B colloidal dispersion) for a duration of 4, 6 ($n = 2$), 8, 18, 23, 25, 36, and 43 days for patients who died, and 21, 23, and 66 days for patients who had disease resolution.
Sipsas[186]	2018	5	Review	Patients with mucormycosis	Disease control	For induction phase of mucormycosis treatment, liposomal amphotericin B or isavuconazole should be continued for at least 3 weeks.

10.7 | Topical antifungals for AIFS

The efficacy of topical antifungals, such as amphotericin irrigations, although reported for chronic rhinosinusitis, is not well studied in the AIFS literature. There are only Level IV and V studies that mentioned their use after sinonasal surgical debridement and in conjunction with systemic therapy for treatment of AIFS. No study has attributed their success for local disease control or survival to topical amphotericin B treatment. Although the reported dose for antifungal irrigation is variable, one in vitro study reported that 200- and 300-μg/mL amphotericin B solutions induced failure of the subcultured fungi to grow at 5 and 6 weeks, respectively.[157] According to the current data, no recommendation can be given regarding the utility of topical antifungals for AIFS. Table 25 summarizes evidence surrounding topical antifungal therapy for AIFS.

Aggregate Grade of Evidence	D (Level 4: 4 studies)
Benefit	Amphotericin B nasal irrigation or packing may help with local disease control.
Harm	There have been no reported harms of topical antifungals, except that it could theoretically worsen sinonasal symptoms.
Cost	There is minimal cost of topical antifungal therapy.
Benefits–Harm Assessment	There are no direct harms or benefits reported from topical antifungal therapy, so it is unclear whether there would be a preponderance of benefit over harm.
Value Judgments	No recommendations can be given due to the low levels of evidence, but balance of increased sinonasal morbidity in the setting of potentially fatal disease should be considered.
Policy Level	Option: There are no clear evidence-based data for these treatments, which are low cost and low risk.
Intervention	It is optional to implement topical antifungal treatment for local management of AIFS (in combination with IV/oral medical treatments), although there are currently no evidence-based benefits.

10.8 | Novel agents for AIFS

Briefly, use of immunomodulating agents to combat fungal infections in patients with hematologic malignancies or similar risk factors represents an evolving frontier of

TABLE 25 Topical antifungal treatments for AIFS.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Shanbag[33]	2019	4	Case series	AIFS (n = 14)	Disease control and survival	All patients were trained to perform nasal irrigations with antifungals postoperatively for 1 week.
Kahana[202]	2007	4	Case series	Sino-orbital mucormycosis with intracranial involvement (n = 2)	Survival	Patients received surgical debridement, systemic amphotericin B and posaconazole, amphotericin B intraorbital infusion, and amphotericin B nasal spray. Patients had disease control but died of hepatorenal failure and intracranial hemorrhage.
Knipping[203]	2007	4	Case series	Invasive aspergillosis involving the skull base (n = 4)	Disease control	Patients received surgical debridement and systemic amphotericin B, itraconazole, and amphotericin B irrigation. Two (50%) had disease control and were free of serious symptoms at 20–24 months.
Kohn[204]	1985	4	Case series	Rhino-orbital mucormycosis (n = 2)	Survival	Patients received surgical debridement, IV amphotericin B, and local amphotericin B irrigation as surgical packing of orbit and sinuses. Patients did not need exenteration and were alive at 3–4 years.

research and include granulocyte colony stimulating factor (G-CSF), interferon, and cellular immunotherapies.[3,4,39] Overall, the use of immunomodulating agents to combat fungal infections is still in an exploratory stage.

11 | MANAGEMENT OF EXTRASINUS EXTENSION IN AIFS

11.1 | Retrobulbar/intraorbital antifungals for orbital involvement

Retrobulbar antifungal injections have been increasingly described as an adjunct to surgical debridement and a potential orbit-sparing treatment for AIFS over the past two decades. Case reports and series have reported outcomes and treatment algorithms for both transcutaneous retrobulbar amphotericin B (TRAMB) injection and orbitotomy with amphotericin B irrigation[205–210] under direct visualization, but highly powered studies of intraorbital antifungal treatment are limited. Such retrobulbar injections are typically performed with liposomal amphotericin B in a 1- to 4-mg/mL concentration. After local anesthetic administration, 1 mL of amphotericin B is injected into the retrobulbar space, typically along the medial orbital wall, and directed into the area of disease. The patient is then monitored for orbital compartment syndrome by the clinician for 5 to 10 minutes and then by the nursing staff. Frequency ranges from multiple injections daily to every 48 to 72 hours, based on clinical response and imaging.[211,212]

In a study of 50 patients with AIFS split into groups based on the introduction of a TRAMB protocol in 2015, Ashraf et al. demonstrated a decreased relative risk of orbital exenteration in the TRAMB group in a multivariate analysis. There was no mortality difference between the two groups, despite a significant difference in rates of orbital exenteration (36.4% before 2015 vs. 9.1% after 2015, $p = 0.014$). The complication rate was 4.3%, and included orbital inflammation, orbital compartment syndrome, and retrobulbar hemorrhage.[211] Arreenich et al. also evaluated retrobulbar amphotericin B injection in 36 patients with AIFS. No significant difference in rates of orbital exenteration or overall survival was found between the injection and control groups on bivariate analysis ($p = 0.19$ and $p = 0.10$, respectively).[212] Although promising, studies on retrobulbar antifungal injections are limited by variability of treatment protocols and small sample size. Table 26 summarizes evidence surrounding use of intraorbital antifungal treatment for AIFS.

Aggregate Grade of Evidence	C (Level 3: 1 study, Level 4: 1 study)
Benefit	Injection route allows for delivery of antifungals directly to the infected space (i.e., orbit), especially in select regions of disease involvement, for local bioavailability while limiting systemic side effects. Injection may be performed at bedside.
Harm	Risk of orbital compartment syndrome, infection/inflammation, or traumatic injury to surrounding neurovascular structures.
Cost	There is a minimal cost of intraorbital antifungal therapy.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	There is limited evidence for use of intraorbital antifungal therapy, with no standardized protocols (e.g., dose, timing) and no seeming advantage for orbital preservation. There is limited harm for patients with complete vision loss and ophthalmoplegia.
Policy Level	Option: Option to consider retrobulbar/intraorbital antifungal therapy for patients with orbital involvement of AIFS.
Intervention	Retrobulbar/intraorbital antifungal therapy may be considered for patients with orbital involvement of AIFS for limited disease, although a thorough discussion of all orbit-directed treatment options should be undertaken.

11.2 | Role of orbitotomy for debridement

Orbitotomy and orbital debridement as an alternative to orbital exenteration have been described in case reports and series[207,210,213–216]; however, this intervention lacks uniform, highly powered studies and requires further research.

11.3 | Role of orbital exenteration

The role of orbital exenteration is the principal dilemma in management of the orbit in AIFS, and multiple studies have identified orbital involvement as a risk factor for poor overall survival.[155,173,217,218] Orbital involvement in AIFS has been reported in the literature to be 50% to 74%,[4,57,155,216,217] and rates of orbital exenter-

TABLE 26 Retrobulbar/intraorbital antifungals.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ashraf[211]	2021	3	Case–control study	50 patients with AIFS split into pre-2015 (conventional treatment) and post-2015 (TRAMB) groups	Risk of exenteration, overall survival	Decreased relative risk of exenteration in the TRAMB group when controlling for cofounders (RR, 0.28; $p = 0.049$). No difference in mortality in the pre- or post-2015 groups. Complication rate was 4.3%.
Arreenich[212]	2021	4	Cohort study	36 patients with AIFS	Risk of exenteration, overall survival	No significant difference in rate of orbital exenteration between control and injection groups ($p = 0.19$). No significant survival difference between the 2 groups ($p = 0.10$).

ation range from 17% to 59%.[12,13,18–22,45,57,147,155,165,216,219] Systematic reviews and cohort studies have evaluated the impact of orbital exenteration on overall survival. Of these seven studies, five identified no significant improvement in overall survival from orbital exenteration.[4,57,147,165,216] However, in a systematic review of 292 patients with orbital mucormycosis, Hargrove et al. found that orbital exenteration improved survival in patients with fever higher than 101.5°F ($p = 0.047$). Of note, patients who developed fever were less likely to survive overall ($s = 0.0031$).[220] Sen et al. performed a retrospective analysis of 2826 patients with novel coronavirus disease-2019 (COVID-19)–associated rhino-orbito-cerebral mucormycosis (137 patients with follow-up >3 weeks), in which orbital exenteration did not improve survival or disease progression in patients with sinonasal and orbital involvement. However, orbital exenteration was associated with improved survival/lack of disease progression in 16 exenterated patients with intracranial involvement ($p = 0.03$).[217] Last, although Kashkouli et al. did not find that orbital exenteration improved overall survival, the mean time of symptom onset to death was significantly longer in patients who underwent orbital exenteration vs. those who did not (80.5 vs. 39.9 days, $p = 0.009$).[147] Although selection bias and sample size continue to limit the study of this disease, these findings overall suggest a limited role of orbital exenteration in improving overall survival in AIFS. Table 27 summarizes evidence surrounding the role of orbital exenteration for AIFS.

Aggregate Grade of Evidence	C (Level 2: 3 studies, Level 4: 4 studies)
Benefit	Complete clearance of infected orbital contents and control of disease process before retrograde spread into the skull base.
Harm	Complete vision loss, cosmetic deformity often requiring reconstruction or future rehabilitation (e.g., prostheses), requires general anesthesia.
Cost	Long-term costs to patient may be high (e.g., ongoing care, protheses, social considerations).
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	There is limited evidence to suggest a survival benefit with orbital exenteration for AIFS. Exenteration may be morbid and disfiguring. The indication for orbital exenteration in an infected eye with intact vision remains unclear.
Policy Level	Option: Option to consider orbital exenteration for patients with orbital involvement of AIFS.
Intervention	Consider orbital exenteration for patients with AIFS with orbital involvement leading to complete vision loss and/or ophthalmoplegia, although it is equally important to discuss that there may not be a survival benefit.

TABLE 27 Role of orbital exenteration.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Turner[4]	2013	2[a]	Systematic review	807 patients with AIFS (398 for analysis of prognostic factors)	Overall survival	Orbital involvement in 50% of patients, and 21% underwent orbital exenteration. Orbital exenteration did not have a significant effect on overall survival ($p = 0.77$).
Hargrove[147]	2006	2[a]	Systematic review	292 patients with orbital mucormycosis	Overall survival	Orbital exenteration did not affect overall survival except in patients with fever >101.5° F, in which case exenterated patients were more likely to survive compared with non-exenterated patients ($p = 0.047$).
Kashkouli[147,220]	2019	3	Cohort study	63 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Orbital exenteration in 20% of patients. Orbital exenteration did not have a significant effect on survival ($p = 0.9$); however, mean time of symptoms to death was significantly longer in patients who underwent exenteration than those who did not (80.5 days vs. 39.9 days, $p = 0.009$).
Sen[217]	2021	4	Cohort study	2826 patients with COVID-19 associated rhino-orbito-cerebral mucormycosis, 137 patients with follow-up >3 weeks	1) Overall survival 2) Disease progression	Orbital exenteration did not improve survival or disease progression in patients with limited or advanced orbital involvement in those with follow-up >3 weeks ($p = 0.99$, $p = 0.24$). Orbital exenteration was associated with improved survival or lack of disease progression in 16 exenterated patients with CNS involvement and follow-up >3 weeks ($p = 0.03$).
Dave[216]	2021	4	Cohort study	58 patients with COVID-19–associated rhino-orbito-cerebral mucormycosis	Overall survival	Orbital exenteration in 38% of patients. Orbital exenteration had no effect on mortality on multivariate regression analysis ($p = 0.6$).
Hirabayashi[57]	2019	4	Cohort study	55 patients with AIFS	1) Overall survival 2) Visual acuity	Orbital involvement in 65% of patients; 16% underwent orbital exenteration. Orbital exenteration did not have a significant effect on overall survival ($p = 0.14$).
Reed[165]	2008	4	Cohort study	41 patients with rhino-orbito-cerebral mucormycosis	Overall survival	Orbital exenteration in 59% of patients. Orbital exenteration did not have a significant effect on overall survival ($p = 0.2$).

[a]Downgraded, due to systematic reviews of case series.

11.4 | Intracranial debridement

Intracranial extension has been reported as a poor prognosticator in AIFS.[4,101,121,221–224] In patients who undergo intracranial debridement, risks of surgery remain high, including cerebrospinal fluid leakage, vascular injury, and morbidity associated with resection of brain parenchyma.[225] Although mortality associated with AIFS is high, surgery may provide improved outcomes in select cases. For instance, Bakhshaee et al. reported a case of AIFS with brain involvement that survived without recurrence after surgical debridement.[37] With few studies reporting the utility of intracranial debridement on survival in AIFS patients with intracranial extension, there appears to be an uncertain role for surgery in limiting recurrence and improving survival,[226–229] particularly considering the challenge of skull base reconstruction after tissue resection from direct sinus-to-brain invasion in the setting of critical illness, active infection, coagulopathy, and the potential need for repeated debridement.

Aggregate Grade of Evidence	D (no dedicated studies)
Benefit	Complete resection of intracranial disease, which may translate to improved survival.
Harm	Significantly increased morbidity given entry into intracranial space (e.g., cerebrospinal fluid leak, intracranial infection).
Cost	Increased costs compared with no surgery.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Conflicting evidence regarding impact of intracranial debridement on overall survival.
Policy Level	No recommendation: Unable to make a recommendation for intracranial surgical resection.
Intervention	Given that intracranial extension in AIFS is a consistently reported poor prognosticator, surgery may provide improved survival in select cases with otherwise poor prognosis, although it is important to counsel patients on risks and possible lack of benefit and share in joint decision-making with other treating teams.

12 | REVERSING IMMUNOSUPPRESSION

12.1 | Diabetic control

Diabetes is a frequently reported comorbidity with a prevalence of 9% to 52% in patients with AIFS.[39,57,105,144,196,210,230] However, the role of diabetes mellitus as a prognostic factor for AIFS is unclear.[230] Several studies reported negative overall survival in patients with diabetes, implicating the depressed humoral and cellular immune responses[230] or elevated glucose as mechanisms of tissue invasion.[133] In one retrospective review of 45 cases of AIFS in 2004, Parikh et al. reported a 40% disease-specific mortality in those with diabetes with increased incidence of intracranial spread (60%), orbital involvement (60%), and neurologic sequelae (66%) among survivors compared with 18% in other immunosuppressive hematologic malignancies.[83] In another retrospective review of 34 patients with AIFS in 2020, Vengerovich et al. reported a 76% overall mortality in patients with diabetes compared with 47% overall mortality in nondiabetic patients, thus supporting diabetes' association with poor outcomes.[56]

The literature is inconclusive, however, with several cohort studies reporting no statistically significant association between diabetes and overall mortality of patients with AIFS.[48,68,105,133] Immunosuppression in diabetes is considered more reversible than other etiologies.[57,210] Therefore, few cohort studies reported improved mortality outcomes in patients with diabetes compared with other causes of immunosuppression. In one retrospective review of 55 patients with AIFS, Hirabayashi et al. reported improved mortality outcomes in the setting of diabetes on bivariate analysis (odds ratio [OR], 0.26; $p = 0.04$).[57] Similarly, a retrospective case series of 45 patients with AIFS demonstrated that, on univariate analysis, diabetes was significantly associated with overall survival vs. those without (hazard ratio [HR], 0.29; $p = 0.01$).[39] The literature assessing mortality outcomes of diabetic patients in AIFS is confounded and requires further study. Table 28 summarizes evidence surrounding glycemic control in AIFS.

Aggregate Grade of Evidence	C (Level 3: 1 study, Level 4: 7 studies)
Benefit	Control of hyperglycemia and its associated vascular effects, reversal of immunosuppression.
Harm	Side effects of medical management.
Cost	Costs associated with pharmacologic management of diabetes.
Benefit–Harm Assessment	Moderate benefit and little harm.
Value Judgments	The evidence supporting management of diabetes in patients with AIFS is mixed. Although increased incidence of intracranial spread and orbital involvement has been described in patients with unmanaged diabetes, other studies suggested little mortality benefit. However, the overall cost and harm is low and potential benefit is high.

TABLE 28 Glycemic control.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kasapoglu[133]	2010	3	Cohort study	26 patients with surgical intervention for AIFS; unspecified DM subtype	Overall survival	No significant difference in overall survival between diabetes patients and those with another immunosuppression (50% mortality in diabetes patients vs. 57% survival overall).
Vengerovich[56]	2020	4	Cohort study	34 patients with AIFS; unspecified DM subtype	Overall mortality	Overall mortality in diabetes patients 76% vs. 47% in patients without diabetes.
Hirabayashi[57]	2019	4	Cohort study	55 patients with AIFS; unspecified DM subtype	Overall survival	Improved mortality outcomes in the setting of DM on bivariate analysis (overall mortality 29%; OR, 0.26; $p = 0.04$).
Foshee[105]	2016	4	Cohort study	27 patients with AIFS, with 52% of patients having diabetes; unspecified DM subtype	Overall mortality	No significant difference in mortality between diabetes patients and those with other causes of immunosuppression (50% mortality; $p = 0.25$).
Kennedy[196]	2016	4	Cohort study	74 patients with mucormycosis, 27% of patients having diabetes; unspecified DM subtype	All-cause mortality	Diabetes not a significant indicator of mortality at 180 days on univariate analysis (50% mortality; $p = 0.41$).
Cho[39]	2015	4	Cohort study	45 patients with AIFS, 51% of patients having diabetes; unspecified DM subtype	1) Overall survival 2) Disease- specific survival	Diabetes was significantly associated with overall survival on univariate analysis (HR, 0.29; $p = 0.01$).
Chen[68]	2011	4	Cohort study	46 patients with AIFS vs. 64 patients with chronic noninvasive sinusitis, 9% of patients having diabetes; unspecified DM subtype	Overall mortality	Diabetes was not an independent prognostic factor of AIFS on univariate analysis (50% mortality; $p > 0.99$).
Parikh[83]	2004	4	Cohort study	43 patients with 45 cases of AIFS; unspecified DM subtype	1) Overall mortality 2) Disease-specific mortality	AIFS-specific mortality in diabetic patients was 40% vs. 18% disease-specific mortality in all patients. Greater mortality and morbidity was seen among diabetic patients with AIFS.

TABLE 29 Leukocyte infusions.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Monroe[41]	2013	4	Case series	29 patients with AIFS	Overall survival	G-CSF or granulocyte infusion was not associated with overall survival on univariate analysis (HR, 1.0; $p = 0.98$).
Parikh[83]	2004	4	Cohort study	43 patients with 45 cases of AIFS	1) Overall mortality 2) Disease-specific mortality	G-CSF or direct granulocyte transfusion given in 51% of patients (13% disease-specific mortality in G-CSF patients vs. 10% overall).
Goering[231]	1988	4	Cohort study	18 immunocompromised patients with AIFS	1) Overall survival 2) Neutrophil recovery	Granulocyte transfusion administered to 72% of AIFS patients, with an overall mortality of 30%.

Aggregate Grade of Evidence	C (Level 3: 1 study, Level 4: 7 studies)
Policy Level	Recommendation: Recommend reversing immunosuppressive effects of uncontrolled diabetes.
Intervention	Strict control of glycemia has a low risk profile and is a recommendation for potential reversal of immunosuppression caused by hyperglycemia.

12.2 | Leukocyte infusions

Neutropenia has been reported to be a risk factor for the development of AIFS[68] and a negative prognostic factor of disease-specific survival in those patients.[84,231] Leukocyte infusions for the treatment of neutropenia are rarely performed and are usually in combination with G-CSF–primed donors.[232] Recovery of absolute neutrophil count has been associated with improved overall survival in AIFS patients,[233,234] but few studies have evaluated the efficacy of direct leukocyte infusion for management of neutropenia in patients with AIFS. Cohort studies reported overall mortality rates of 26% to 30% with containment of infection after granulocyte transfusion, providing support for this treatment modality.[83,231] However, in one cohort study of 29 patients with AIFS, granulocyte infusion was not associated with improved overall survival on univariate analysis (HR, 1.0; $p = 0.98$).[41] Overall, there are very few high-quality studies of leukocyte infusion therapy for AIFS patients in the literature, and this intervention requires further study. Table 29 summarizes evidence surrounding the role of leukocyte infusions in AIFS.

Aggregate Grade of Evidence	C (Level 4: 3 studies)
Benefit	Recovery of absolute neutrophil count, reduction in mortality, and containment of infection.
Harm	Injection-site morbidity and associated drug reactions.
Cost	Costs of infusions and associated therapy.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Leukocyte infusions for the treatment of neutropenia are rarely performed and are usually in combination with G-CSF–primed donors. The literature has very few high-quality studies of leukocyte infusion therapy alone for AIFS patients.
Policy Level	Option: Option for leukocyte infusions in AIFS treatment.
Intervention	Leukocyte infusions can be considered in patients with neutropenia, likely in combination with G-CSF.

12.3 | Granulocyte colony stimulating factor

G-CSF is indicated in patients with neutropenia, which occurs often after undergoing chemotherapy treatment, by stimulating growth and differentiation of neutrophil progenitor cells.[235,236] As such, it is a viable therapy in neutropenic patients for the management of AIFS with a reported overall response rate of 50% to 90%.[57,237] Few cohort studies suggested that positive G-CSF response was a favorable prognostic sign of AIFS, with one multi-

institutional review of 114 patients with AIFS showing a 70% reduction in 1-month mortality but no significant difference in 3-month mortality with immunostimulating therapies.[83,89,233] However, multiple cohort studies conversely indicated that G-CSF was not a predictor of short-term survival[6] or overall survival.[41] In one systematic review of 103 pediatric AIFS patients in 2016, Smith et al. concluded that G-CSF treatment was not a predictor of overall mortality.[18] Although G-CSF is a promising theoretical adjunctive therapy for neutropenia, its efficacy in the setting of AIFS requires further investigation. Table 30 summarizes evidence surrounding the role of G-CSF in AIFS.

Aggregate Grade of Evidence	B (Level 3: 1 study; Level 4: 4 studies)
Benefit	Stimulation of neutrophil progenitor cells with potential increase in neutrophil count.
Harm	Injection-site morbidity and associated drug reactions.
Cost	Costs of infusions and associated therapy.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	Although G-CSF is a promising theoretical adjunctive therapy for neutropenia, its efficacy in the setting of AIFS requires further study.
Policy Level	Option: Option for G-CSF in AIFS treatment.
Intervention	G-CSF may be considered in AIFS patients for management of neutropenia.

12.4 | Other immunomodulating agents

Interferon-γ can enhance antifungal activity of macrophages and polymorphonuclear neutrophils and may reduce fungal burden in murine aspergillosis.[238] There are successful clinical applications of interferon-γ as adjunctive therapy in immunocompromised patients with aspergillosis.[239–241] Cellular immunotherapy, such as adoptive transfer of anti-*Aspergillus* T cells has been tested in clinical studies with results showing enhanced control of *Aspergillus* antigenemia and reduced mortality.[242] D-Chimeric antigen receptor (CAR) T cells with specificity for β-1,3-D-glucan and effective against *A fumigatus* are also under development.[243] Overall, the use of immunomodulating agents to combat fungal infections is still at an exploratory stage. Table 31 summarizes evidence surrounding the role of other immunomodulating agents in AIFS.

TABLE 30 Use of granulocyte stimulating factor.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Smith[18]	2016	2	Systematic review	103 pediatric AIFS patients	Mortality rate	G-CSF treatment was not a predictor of overall mortality on univariate analysis.
Roxbury[6]	2017	4	Cohort study	54 patients with AIFS	Short-term survival	Forty-three percent of patients received G-CSF. No statistical difference in short-term survival between patients who received G-CSF and those who did not (68% vs. 70%, respectively, $p = 0.9$).
Monroe[41]	2013	4	Case series	29 patients with AIFS	Overall survival	G-CSF or granulocyte infusion was not associated with overall survival on univariate analysis (HR, 1.0; $p = 0.98$).
Parikh[83]	2004	4	Cohort study	43 patients, with 45 cases of AIFS	1) Overall mortality 2) Disease-specific mortality	G-CSF or direct granulocyte transfusion in 51% of patient (13% disease-specific mortality in G-CSF patients vs. 10% overall).
Gillespie[89]	1998	4	Cohort study	25 patients with AIFS	1) Overall survival 2) WBC increase	Positive response to G-CSF was a favorable prognostic sign in all patients receiving G-CSF treatment. These patients also demonstrated an increase in WBC of $>0.50 \times 10^9$/L.

TABLE 31 Other imunomodulating agents.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Perruccio[242]	2005	2	Randomized controlled trial	23 haploidentical transplant patients with invasive aspergillosis	Overall survival	Ninety percent resolution of infection in patients receiving *Aspergillus*-specific T-cell therapy vs. 54% in the control group.
Armstrong-James[241]	2010	4	Case series	7 kidney transplant patients with AIFS	Overall survival	Exogenous interferon-γ in combination with antifungal drugs may induce faster clearance of fungal infections.

Aggregate Grade of Evidence	**C (Level 1: 1 study; Level 4: 1 study)**
Benefit	Enhancement of antifungal macrophage and neutrophil activity, enhanced control of infection, and reduced mortality.
Harm	Side effects of specific agents.
Cost	Economic costs of exploratory immunomodulating agents.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	Interferon-γ, anti-*Aspergillus* T cells, and CAR T cells have shown possible benefit in the control of AIFS.
Policy Level	Option: Option for several immunomodulating agents that are still under investigation.
Intervention	The use of other immunomodulating agents to combat fungal infections is still in an exploratory stage.

12.5 | Posttransplant

Stem cell transplant (SCT), bone marrow transplant (BMT), and solid-organ transplant are immunosuppressive conditions that may predispose to the development of AIFS. Patients with prolonged neutropenia are candidates for SCT or BMT, which subsequently increases the susceptibility of these patients to AIFS.[180,244] In contrast, solid-organ transplant susceptibility is largely due to the postoperative immunosuppressive regimen.[245] Cohort studies have reported overall mortality for patients with AIFS after receiving SCT or BMT to be 33% to 100%.[52,246,247] In a case–control study of 46 patients with AIFS, Chen et al. concluded that SCT was not an independent prognostic factor of AIFS ($p = 0.68$).[68] Kennedy et al. similarly reported no statistically significant association between BMT and AIFS on univariate analysis ($p = 0.68$).[48]

Two cohort studies have reported overall survival in patients with AIFS after receiving a solid-organ transplant to be 25% to 100%.[11,27,83,155] However, these studies are limited by sample size and do not report statistical significance. A cohort study of 45 patients with AIFS in 2015 showed that there was no statistically significant association between patients with organ transplant and overall or disease-specific survival (HR, 0.72; $p = 0.75$).[39] The lack of a statistically significant association between solid-organ transplant and AIFS is supported by a study of 55 patients with AIFS in 2019 (OR, 0.16; $p = 0.12$).[57] Overall, the lack of statistical significance limits the assessment of outcomes in posttransplant AIFS patients. Table 32 summarizes

TABLE 32 Posttransplant etiologies.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hirabayashi[57]	2019	4	Cohort study	55 patients with AIFS	Overall survival	Nine percent of patients received organ transplant with an overall survival of 100%. Trend was toward improved mortality outcomes, although not statistically significant on bivariate analysis (OR, 0.16; $p = 0.12$).
Tzelnick[245]	2019	4	Cohort study	4562 solid-organ transplant recipients	1) Surgical intervention 2) Overall survival	AIFS developed in 0.04% of the solid-organ transplant patients.
Kohashi[246]	2018	4	Case series	9 cases of *E rostratum* sinusitis	Overall survival	Five neutropenic patients receiving stem cell transplant with 100% mortality compared with 4 immunocompetent patients with 100% survival.
Trief[155]	2016	4	Cohort study	24 patients with invasive fungal disease of sinus and orbit	Overall survival	Eight percent of patients with sinus involvement having received solid-organ or HSCT; 100% survival in transplant patients with only sinus involvement compared with 0% survival in those with orbital involvement; 25% posttransplant overall survival.
Cho[39]	2015	4	Cohort study	45 patients with AIFS	1) Overall survival 2) Disease- specific survival	No statistically significant association between patients with organ transplant and overall or disease-specific survival (HR, 0.72; $p = 0.75$)
Chen[68]	2011	4	Case–control	46 patients with AIFS vs. 64 patients with chronic noninvasive sinusitis	Overall mortality	Thirteen percent of patients received allogeneic stem cell transplant. Stem cell transplant was not an independent prognostic factor of AIFS (50% mortality, $p = 0.68$).
Parikh[83]	2004	4	Cohort study	43 patients with 45 cases of AIFS	1) Overall mortality 2) Disease-specific mortality	Mortality 0% in patients with solid-organ transplants.
Kennedy[48]	1997	4	Cohort study	1692 bone marrow transplant (BMT) patients, 26 patients with AIFS posttransplant	Overall mortality	Incidence of AIFS 1.7% in BMT patients, with a mortality of 61.5%. BMT was not an independent prognostic factor of AIFS infection on univariate analysis ($p = 0.68$).
Choi[247]	1995	4	Cohort study	80 pediatric BMT patients	Disease-specific mortality	*Aspergillus* sinusitis with 4% incidence in patients receiving BMT, with 0% disease-specific mortality.
Drakos[52]	1993	4	Cohort study	456 BMT patients	Disease-specific mortality	Incidence of AIFS 2.6% in BMT patients, with a disease-specific mortality of 54%.

evidence surrounding management of posttransplant patients in AIFS.

Aggregate Grade of Evidence	C (Level 4: 10 studies)
Benefit	History of transplant is a clear source of immunosuppression, allowing for stopping immunosuppressive agents as a possible intervention.
Harm	Limited options for intervention to reverse immunosuppression after transplantation given risks of transplant rejection.
Cost	Potentially high if rejection/failure occurs.
Benefit–Harm Assessment	Balance of benefit and harm.
Value Judgments	It is important to involve transplant team and discuss with patient regarding the risks and benefits of withholding immunosuppressive agents, which may restore immune function at the expense of transplant rejection/failure.
Policy Level	Option: Option to withhold immunosuppressive agents in setting of AIFS in the posttransplant state.
Intervention	Clinical judgment should be exercised and thorough discussion held with the patient and transplant team regarding holding immunosuppression in the setting of AIFS.

12.6 | COVID-19

Elevated iron levels in COVID-19 patients are increasingly implicated in the development of AIFS.[217] Case reports have reported the mortality of AIFS in post–COVID-19-positive patients to be near 36% to 37%.[29,153,256] One retrospective cohort study reported that chronic disease such as chronic kidney disease, leukemia, or immunosuppressive drugs were risk factors in the development of COVID-19 infection in AIFS patients ($p < 0.05$).[248] However, high-quality evidence regarding the overall survival of these patients is limited. In 2021, a cohort study of 31 patients with rhino-orbital mucormycosis showed that COVID-19 history was not a predictive factor of survival in patients with mucormycosis ($p = 0.30$).[249] Two multicenter cohort studies following 58 and 2826 COVID-19–associated rhino-orbital mucormycosis patients found overall survival to be 66% to 86%.[216,217] In those studies, immunosuppressive corticosteroid use was a reported independent risk factor for unfavorable clinical outcomes and for the development of rhino-orbital mucormycosis in COVID-19 patients.[216,217] Table 33 summarizes evidence surrounding COVID-19 as an etiologic factor in AIFS.

Aggregate Grade of Evidence	C (Level 4: 3 studies)
Benefit	Treatment of COVID-19, if indicated, is potentially lifesaving. Understanding COVID-19 as new risk factor allows for possible preventive measures for patients at higher risk for AIFS given other comorbidities (e.g., diabetes, transplant).
Harm	Limited options for intervention.
Cost	Potentially high if infection becomes severe, beyond whether AIFS develops.
Benefit–Harm Assessment	Preponderance of benefit over harm.
Value Judgments	AIFS related to COVID-19 is a very new discovery and there is growing evidence in this area. In addition, consideration of risks of corticosteroids, which are commonly used in severe COVID-19 infection in this setting, should be discussed with the patient and multidisciplinary team.
Policy Level	Recommendation: Recommendation for treatment of COVID-19.
Intervention	Despite currently limited evidence, as more treatments are developed for COVID-19, this may eventually impact AIFS outcomes.

13 | OUTCOMES AND SURVIVAL

AIFS outcomes have been historically poor,[51,35,54] and recent estimates for overall survival in adult and pediatric AIFS patients range from 40% to 80%.[4,5,18,83,250] However, disease-specific survival is often higher,[41,23,83] highlighting that AIFS patients typically have significant associated medical comorbidities. This section reviews the most recent evidence regarding AIFS survival outcomes.

13.1 | Underlying immunosuppression

Nearly all patients with AIFS present with some form of underlying immunosuppression, with diabetes and hematologic malignancies being among the most common.[4,5,18,83,250] Turner et al. reported patients with diabetes had lower odds of mortality (OR, 0.492; overall survival rate: 49.7%) in their systematic review of more than 800 AIFS patients.[4] In comparison those who underwent an early diagnosis protocol had a disease-specific

TABLE 33 COVID-19.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ravani[249]	2021	4	Cohort study	31 patients with rhino-orbital mucormycosis	Overall survival	COVID-19 positivity 61.2% in study group. COVID-19 history was not a predictive factor of survival in patients with mucormycosis ($p = 0.30$).
Dave[216]	2021	4	Cohort study	58 patients with rhino-orbital-cerebral mucormycosis after COVID-19 infection	Overall survival	Overall survival 66%. Corticosteroid use and uncontrolled diabetes were predictive factors for unfavorable clinical outcomes on bivariate and multivariate analysis, whereas CNS involvement was a predictive factor for mortality on multivariate analysis ($p = 0.03$).
Sen[217]	2021	4	Cohort study	There were 2826 patients with COVID-19–associated rhino-orbital-cerebral mucormycosis	Overall survival	Overall survival 86%. Corticosteroid use and diabetes are significant predisposing factors for the development of COVID-19 in ROM patients.

survival rate increase from 57.1% to 83.5%.[23] However, diabetic ketoacidosis at presentation has been shown to have significant associations with increased mortality.[8] Hematologic malignancy patients appear to have worse survival outcomes,[5,7,250] with one multi-institutional study noting a 3.3-fold increased risk of death at 3 months.[5] A 2018 epidemiologic study of inpatient hospitalizations in the United States did not identify an association between diabetes or type of immunocompromising illness with AIFS infection, but the authors acknowledged that the rates of immunocompromising conditions are likely underreported in the database used.[251] Furthermore, overall survival appears to be related to progression or recurrence of the underlying malignancy rather than AIFS, as AIFS-specific survival tends to be higher in these patients.[23,83] Studies evaluating other causes of immunosuppression are scarce with low numbers of patients with associated conditions, but patients with recent bone marrow transplantation have worse survival (61.5%),[5,83] whereas human immunodeficiency virus/acquired immunodeficiency syndrome and renal transplant patients appear to have improved survival.[144] Although neutropenia has traditionally been an associated risk factor for development of AIFS, it does not appear to be predictive of survival outcomes in AIFS patients.[5,27] Nevertheless, recovery of ANC in neutropenic patients appears to be an important prognostic factor.[15,44,48,83] Table 34 summarizes evidence surrounding the impact of the source of immunosuppression on survival in AIFS.

Aggregate Grade of Evidence: B (Level 2: 2 studies; Level 3: 6 studies; Level 4: 6 studies).

13.2 | Organism

The most common causative organisms for AIFS are from the *Aspergillus* genus and *Mucoraceae* family (35% and 24%, respectively).[4,5,250] *Mucoraceae*, which include *Mucor*, *Rhizopus*, and *Rhizomucor*, appear to be more common among diabetic AIFS patients, likely due to their affinity for acidotic and high glucose environments.[28,35,51] Less frequently encountered organisms, such as *Candida*, *Fusarium*, *Scedosporium*, can also less commonly cause AIFS, and Wandell et al. found them to be independently associated with worse survival (HR of 3.1 at 1 month and HR of 2.4 at 3 months).[5] However, Shintani-Smith et al. did not find an association between fungal organism and mortality in a U.S. national inpatient database.[251] Survival outcomes are variable between the included studies,[4,5,7,56,144,250] and the impact of offending organisms on AIFS survival remains unclear. Table 35 summarizes evidence surrounding the impact of the underlying organism on survival in AIFS.

Aggregate Grade of Evidence: C (Level 2: 2 studies; Level 3: 5 studies; Level 4: 3 studies).

13.3 | Timing of intervention

Screening protocols aiming to reduce time to treatment have been investigated in single institution studies with improvement in disease morbidity or survival outcomes.[14,23,24,63] Several studies have demonstrated improved survival in patients undergoing surgery within

TABLE 34 Causes of immunosuppression and impact on survival.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Smith[18]	2016	2	Systematic review	Pediatric AIFS patients ($n = 103$ patients in 12 studies)	Overall survival	Mortality for pediatric AIFS was 46%. The only presenting symptom of facial pain was a negative predictor of overall survival. Neutropenia from an underlying malignancy with an ANC <600 is the most frequent setting of pediatric AIFS, particularly if present for >2 weeks before onset.
Turner[4]	2013	2	Systematic review	AIFS patients ($n = 807$ patients in 52 studies)	Overall survival	Overall survival 49.7%. Univariate analysis: renal/liver failure, altered mental status, and intracranial extension associated with worse prognosis; diabetes, surgical management, or receiving liposomal amphotericin B associated with improved prognosis. Multivariate analysis: advanced age and intracranial involvement were independent negative factors; diabetes and surgical management were positive factors.
Shintani-Smith[251]	2022	3	Observational study	AIFS patients ($n = 340$) from 2018 National Inpatient Sample	1) Overall survival 2) Patients' demographics and comorbidities	Caucasian (50.8%), followed by Hispanic (23.9%), Black (17.9%), and other races (7.5%); 67.7% were immunocompromised, with diabetes/long-term insulin use in 55.8%. Mortality was 23.5%
Gardner[27]	2021	3	Retrospective cohort	AIFS patients ($n = 21$)	Overall survival	Overall survival 71% and 52% at 1 and 3 months, respectively. Current smoking and lack of rhinology subspecialty involvement associated with increased risk of death at 3 months. ANC, disease extent, and fungus species showed no significant difference in survival.
Burton[250]	2019	3	Ecological	Adults with AIFS in the National Inpatient Sample database ($n = 979$)	Inpatient mortality	Mucormycosis, pneumonia, hematologic disorders, and age (per decade) associated with increased odds of inpatient mortality on multivariate analysis. Diabetes associated with lowest odds of inpatient mortality.
Wandell[5]	2018	3	Retrospective cohort	Adult AIFS patients ($n = 114$)	Overall survival	Hematologic malignancy, recent chemotherapy, atypical organisms, and cavernous sinus extension associated with worse survival on multivariate analysis. Increasing HbA1C% and surgical debridement associated with improved survival. ANC was not associated with prognosis. Immunostimulating therapy associated with 70% reduction in mortality at 1 month.

(Continues)

TABLE 34 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Fernandez[23]	2018	3	Retrospective cohort	AIFS patients ($n = 19$)	1) Disease-specific mortality at 24 months 2) Time to surgical intervention	Disease-specific survival rate increased from 57.1% to 83.3% after initiation of early diagnosis protocol. Application of protocol significantly reduced the delay for diagnosis and appropriate treatment by an average of 7.3 days. Decreased interval from symptom onset to surgery correlated with improved survival.
Davoudi[7]	2015	3	Retrospective cohort	AIFS patients with hematologic malignancy ($n = 44$)	1) All-cause mortality 2) Disease-specific mortality	Relapsed and/or refractory hematologic malignancy was independent risk factor for 6- and 12-week AIFS-specific mortality. *Aspergillus* infection was an independent risk factor for 12-week all-cause and disease-specific mortality. ANC <100/μL and lymphocyte count <200/μL were associated with increased 12-week IMS-attributable and 6-week all-cause mortality, respectively.
Raizada[8]	2018	4	Case series	AIFS patients with DM ($n = 22$)	1) Overall survival 2) Radiographic response to treatment	Ketoacidosis at presentation associated with mortality in diabetics. Intracranial disease and decreased hemoglobin associated with mortality. No patients had radiologic improvement at day 30 imaging (including those who subsequently improved).
Green[15]	2016	4	Case series	Pediatric AIFS patients ($n = 14$)	Overall survival	Likelihood of recovery of ANC to normal levels was the only positive prognostic indicator for survival. Role of endoscopic sinus surgeries in survival is indeterminate, as there was no statistical difference between the number of surgeries performed and mortality.
Valera[144]	2011	4	Case series	AIFS patients ($n = 32$)	Overall survival	Poor prognosis was related to the extent of AIFS and to the underlying disease. Patients with aplastic anemia and diabetes had the worst outcomes. Patients with AIDS/HIV or renal insufficiency presented a better prognosis, hematologic malignancy had an intermediate prognosis. Fungal organism did not correlate with clinical outcome.

(Continues)

TABLE 34 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Süslü[44]	2009	4	Case series	AIFS patients ($n = 19$)	Overall mortality	Mortality was 43% in patients treated surgically. Aggressive surgical debridement and intravenous antifungal drugs are the mainstays of AIFR treatment, but disease prognosis depends on recovery from the underlying disease. Recovery of ANC appears to be the most important prognostic factor.
Parikh[83]	2004	4	Case series	AIFS patients ($n = 43$)	1) Overall mortality 2) Disease-specific mortality	Mortality from AIFS among diabetic patients (40%) was significantly higher than in HM (11%), long-term steroid users (33%), and solid-organ transplant patients (0%). Mortality from *Mucor* was greater than mortality from *Aspergillus* (29% vs. 11%), regardless of etiology of immunosuppression. Recovery of ANC is the most predictive indicator of survival. All patients who had their ANC return to normal recovered from AIFS.
Kennedy[48]	1997	4	Case series	BMT patients with AIFS ($n = 26$)	1) Overall survival 2) Effect of radical vs. limited surgery	Incidence of AIFS in BMT patients was 1.7%, and mortality was 61.5%. The only statistically and clinically significant predictor of outcome was the presence of orbital and/or cranial involvement. No significant difference in outcomes based on extent of surgical resection.

7 days of AIFS diagnosis (increased from 57.1% to 83.5%),[20,23,51] and others have shown significantly worse outcomes in patients with treatment delays of over 14 days from disease onset (increased death rate from 30.9% to 33.3%).[21,122] Table 36 summarizes evidence surrounding the impact of timing of intervention on survival in AIFS.

Aggregate Grade of Evidence: C (Level 3: 6 studies; Level 4: 2 studies).

13.4 | Extent of disease involvement

Disease extension affects clinical decision-making and patient outcomes in AIFS. Roxbury et al. proposed a staging system to stratify the extent of disease. They demonstrated that patients with disease limited to the nasal cavity were more likely to have complete surgical resection and improved survival.[6] However, involvement of the nasal septum or bilateral disease have been associated with significantly worse outcomes.[36,39,105,144,252] Patients with extrasinus extension to the orbit (33% mortality), skull base (50% mortality), cavernous sinus (HR of 2.7 at 1 month), and brain (100% mortality) appear to have worse survival,[3,5,41,49,173,211,253] yet only intracranial involvement was independently association with worse prognosis in the largest systematic review to date.[4] Table 37 summarizes evidence surrounding the impact of the extent of disease involvement on survival in AIFS.

Aggregate Grade of Evidence: C (Level 2: 1 study; Level 3: 5 studies; Level 4: 8 studies).

14 | FOLLOW-UP AND SURVEILLANCE

In this review, no studies primarily evaluated timing of disease surveillance as a primary outcome, as there are limited data within this realm. Although more studies are needed in this area, we summarize protocols mentioned in several studies.

TABLE 35 Type of organisms affecting survival in AIFS.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Vaughan[35]	2018	2	Systematic review and meta-analysis	Patients with rhino-orbital-cerebral mucormycosis ($n = 175$)	1) Overall survival 2) Interval to treatment	Overall survival of 59.5%. Survival in patients with chronic renal disease and leukemia had improved. Facial necrosis and hemiplegia were poor prognostic indicators (33% and 39% survival rates, respectively). Early commencement of medical treatment related to better survival outcomes (61% if commenced within first 12 days of presentation vs. 33% if after 13 days). Timing of surgery had less of an effect on overall survival.
Turner[4]	2013	2	Systematic review	AIFS patients ($n = 807$ patients in 52 studies)	Overall survival	Overall survival of 49.7%. On univariate analysis: renal/liver failure, altered mental status, and intracranial extension associated with worse prognosis; diabetes, surgical management, or receiving liposomal amphotericin B associated with improved prognosis. Multivariate analysis: advanced age and intracranial involvement were independent negative factors; diabetes and surgical management were positive factors.
Shintani-Smith[251]	2022	3	Observational study	AIFS patients ($n = 340$) from 2018 National Inpatient Sample	1) Overall survival 2) Patients' demographics and comorbidities	Caucasian (50.8%), followed by Hispanic (23.9%), Black (17.9%), and other races (7.5%); 67.7% immunocompromised with diabetes/long-term insulin use in 55.8%. Mortality was 23.5%.
Burton[250]	2019	3	Ecological	Adults with AIFS in the National Inpatient Sample database ($n = 979$)	Inpatient mortality	Mucormycosis, pneumonia, hematologic disorders, and age (per decade) associated with increased odds of inpatient mortality on multivariate analysis. Diabetes associated with lowest odds of inpatient mortality.
Gür[28]	2021	3	Retrospective cohort	Patients with rhinocerebral mucormycosis ($n = 24$)	Disease-specific mortality	Extent of disease was only prognostic for mortality (orbital or cerebral involvement related to a poor prognosis). Serum glucose level cutoff of 360 mg/dL revealed an 83.3% sensitivity and 83.3% specificity for mortality outcome for diabetes patients with mucormycosis.

(Continues)

TABLE 35 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wandell[5]	2018	3	Retrospective cohort	Adult AIFS patients ($n = 114$)	Overall survival	Hematologic malignancy, recent chemotherapy, atypical organisms, and cavernous sinus extension associated with worse survival on multivariate analysis. Increasing HbA1C% and surgical debridement associated with improved survival. ANC was not associated with prognosis. Immunostimulating therapy associated with a 70% reduction in mortality at 1 month.
Davoudi[7]	2015	3	Retrospective cohort	AIFS patients with hematologic malignancy (n = 44)	1) All-cause mortality 2) Disease-specific mortality	Relapsed and/or refractory hematologic malignancy was an independent risk factor for 6- and 12-week AIFS-specific mortality. *Aspergillus* infection was an independent risk factor for 12-week all-cause and disease-specific mortality. ANC <100/μL and lymphocyte count <200/μL were associated with increased 12-week IMS-attributable and 6-week all-cause mortality, respectively.
Vengerovich[56]	2020	4	Case series	AIFS patients ($n = 34$)	Overall mortality	Overall mortality 61.8%, with inverse correlation between mortality and number of comorbidities and positive correlation with extent of disease compared with disease localized to sinuses.
Valera[144]	2011	4	Case series	AIFS patients ($n = 32$)	Overall survival	Poor prognosis was related to the extent of AIFS and to the underlying disease. Patients with aplastic anemia and diabetes had the worst outcomes. Patients with AIDS/HIV or renal insufficiency presented with a better prognosis; hematologic malignancy had intermediate prognosis. Fungal organism did not correlate with clinical outcome.
Yohai[51]	1994	4	Case series	Patients with rhino-orbital-cerebral mucormycosis ($n = 144$)	Overall survival	Delayed diagnosis, leukemia, renal disease, bilateral sinus involvement, hemiparesis, and treatment with deferoxamine were associated with worse survival. Survival declined if interval to treatment was >6 days; no survivors after 12 days of disease in those without diabetes, and more gradual decline in diabetics.

TABLE 36 Timing of intervention and impact on survival.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Alejandro[20]	2020	3	Retrospective cohort	Pediatric AIFS patients ($n = 18$)	1) All-cause mortality 2) Disease-specific mortality	Time between diagnosis and surgery of >7 days was a risk factor for all-cause mortality and disease-specific mortality.
Malleshappa[21]	2020	3	Prospective cohort	AIFS patients ($n = 51$)	1) Number of surgeries 2) Overall survival	Difference in outcomes with a single surgery vs. multiple surgeries was not significant. No association was found between stage of disease and outcome. The overall survival rate was 68.2%; 73.5% survival rate for diabetics alone.
Silveira[63]	2019	3	Retrospective cohort	AIFS patients ($n = 43$)	1) Overall mortality 2) Frozen section biopsy accuracy	Early screening protocol was associated with decreased mortality, from 50% to 30.2%. Better outcomes were observed in patients with disease limited to the turbinates and in those with higher peripheral neutrophil count. Frozen section biopsy positivity correlated with FFPE findings for fungi detection, with a sensitivity of 90.6%, specificity of 72.7%, and accuracy of 86.0%.
Fernandez[23]	2018	3	Retrospective cohort	AIFS patients ($n = 19$)	1) Disease-specific mortality at 24 months 2) Time to surgical intervention	Disease-specific survival increased from 57.1% to 83.3% after initiation of early diagnosis protocol. Application of protocol significantly reduced the delay for diagnosis and appropriate treatment by an average of 7.3 days. Decreased interval from symptom onset to surgery correlated with improved survival.
Cohn[14]	2016	3	Retrospective cohort	Pediatric hematologic malignancy patients with AIFS ($n = 50$)	1) Overall mortality 2) Efficacy of early intervention protocol	Sixty percent mortality in prescreening cohort; 23% mortality after early screening protocol was initiated.
DelGaudio[24]	2009	3	Non-concurrent cohort	AIFS patients ($n = 24$)	1) Long-term morbidity 2) Overall mortality	Fewer sites of involvement at diagnosis, fewer surgeries, and less long-term morbidity with earlier diagnosis. No change in mortality with earlier diagnosis/intervention—thought to be related to recovery of ANC.
Piromchai[122]	2014	4	Case series	Patients with AIFS ($n = 45$) and CIFS	1) Time to treatment 2) Overall mortality	All mortalities were in the AIFS group; all patients in chronic AIFS group survived. Time to treatment was the most statistically significant predictor for mortality, and definitive treatment should be conducted within 14 days.
Yohai[51]	1994	4	Case series	Patients with rhino-orbital-cerebral mucormycosis ($n = 144$)	Overall survival	Delayed diagnosis, leukemia, renal disease, bilateral sinus involvement, hemiparesis, and treatment with deferoxamine were associated with worse survival. Survival declined if interval to treatment was >6 days; no survivors after 12 days of disease in nondiabetes patients, with a more gradual decline in patients with diabetes.

TABLE 37 Extent of disease and impact on survival.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Turner[4]	2013	2	Systematic review	AIFS patients ($n = 807$ patients in 52 studies)	Overall survival	Overall survival of 49.7%. Univariate analysis: renal/liver failure, altered mental status, and intracranial extension associated with worse prognosis; diabetes, surgical management, or receiving liposomal amphotericin B associated with improved prognosis. Multivariate analysis: advanced age and intracranial involvement were independent negative factors; diabetes and surgical management were positive factors.
Al-Obaidi[252]	2021	3	Retrospective cohort	Patients with invasive mucormycosis; subset with AIFS ($n = 24$)	Overall survival	No significant difference in mortality between solid-organ transplant patients and those with diabetes. Higher mortality in patients with bilateral disease. No difference in mortality outcomes among the different types of antifungal therapies administered.
Ashraf[211]	2021	3	Retrospective cohort	AIFS patients with imaging evidence of orbit involvement ($n = 50$)	1) Rate of orbital exenteration 2) Overall mortality	Patients with retrobulbar amphotericin injection had lower rates of exenteration, but similar mortality rates.
Candoni[3]	2019	3	Retrospective cohort	Hematologic malignancy patients with cerebral or paranasal invasive fungal infection ($n = 89$)	1) Overall and disease-attributable mortality 2) Response to antifungal therapy	Overall mortality was 69% but disease-attributable mortality was 33%. Overall response rate to antifungal therapy (complete or partial response) was 57%, without significant differences between patients with cerebral or paranasal sinus invasive fungal disease.
Wandell[5]	2018	3	Retrospective cohort	Adult AIFS patients ($n = 114$)	Overall survival	Hematologic malignancy, recent chemotherapy, atypical organisms, and cavernous sinus extension associated with worse survival on multivariate analysis. Increasing HbA1C% and surgical debridement associated with improved survival. ANC was not associated with prognosis. Immunostimulating therapy associated with 70% reduction in mortality at 1 month.
Cho[39]	2015	3	Retrospective cohort	AIFS patients ($n = 45$)	Overall survival	Underlying hematologic malignancy associated with worse overall survival and diabetes associated with improved survival. Severe neutropenia (ANC <500) and elevated CRP were related to poor prognosis. Initial presentation with facial swelling, involvement of nasal septum, or shorter symptom duration were also associated with survival reduction. Multivariate analysis showing CRP >5.50 mg/dL was an independent prognostic factor in patients with AIFS.

(Continues)

TABLE 37 (Continued)

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Roxbury[6]	2017	4	Case series	AIFS patients ($n = 52$)	1) Survival at hospital discharge 2) Complete surgical resection	Complete surgical resection was the only factor in this study associated with survival. Staging system was proposed; decreased survival associated with higher stage (essentially, increased disease extent).
Ergun[36]	2017	4	Case series	AIFS patients ($n = 19$)	Overall survival	Overall survival rate was 38.8%. Patients with type 2 diabetes and those with multiple etiologies causing immunosuppression had the lowest survival. Cessation of corticosteroids and regulating blood glucose levels in patients with immunosuppression from corticosteroid use resulted in 75% survival.
Foshee[105]	2016	4	Case series	AIFS patients ($n = 27$)	Overall survival	Overall mortality was 57.7% within 1 year, and 66.7% of fatalities occurred within 1 month of diagnosis. Nasal septum involvement was associated with worse mortality.
Monroe[41]	2013	4	Case series	AIFS patients ($n = 29$)	1) Disease-specific survival 2) Overall survival	Disease-specific survival was 57%; 6-month overall survival was 17%. Intracranial and ethmoid sinus involvement were significantly linked with short-term disease-related mortality. Intracranial involvement and cranial neuropathy at presentation were significantly associated with shortened overall survival. Surviving patients at risk for major long-term sinonasal complications.
Valera[144]	2011	4	Case series	AIFS patients ($n = 32$)	Overall survival	Poor prognosis was related to the extent of AIFS and to the underlying disease. Patients with aplastic anemia and diabetes had the worst outcomes. Patients with AIDS/HIV or renal insufficiency presented with better prognosis, and hematologic malignancy had intermediate prognosis. Fungal organism did not correlate with clinical outcome.
Peterson[173]	1997	4	Case series	AIFS patients ($n = 28$)	Overall mortality	Mortality rate was 16.7% in diabetics, 40% in hematologic malignancy patients, and 60% in patients with immunosuppression. Thirty-three percent overall mortality if orbital symptoms/involvement; 14% mortality if no orbital involvement.
Iwen[49]	1997	4	Case series	AIFS patients ($n = 17$)	1) Overall survival 2) Treatment outcome 3) Extent of disease	Overall survival of 47%. The survival rate among patients treated with amphotericin B and surgery was 60%, whereas that among patients who did not undergo surgery was only 28.6%. All 3 patients who underwent enucleation of an eyeball survived and were disease-free.
Nussbaum[253]	1994	4	Case series	Patients with rhinocerebral mucormycosis ($n = 11$)	1) Overall mortality	Overall mortality rate was 43%. Patients with intracranial disease had 100% mortality. All patients with localized sinonasal disease survived.

14.1 | Bedside endoscopy

Given the aggressive nature of disease, Gillespie et al. recommended weekly nasal endoscopy after initiating antifungal treatment and surgical debridement until reversal of neutropenia and monthly endoscopy up to 3 months after immune function recovery.[89] Other studies similarly recommend weekly or biweekly postoperative debridement either in clinic or in the operating room until disease control has been achieved.[21,174] Otto et al. advocated for longer follow-up with regular nasal endoscopy and debridement until re-mucosalization and recovery of normal sinus physiology are complete, as 62% of AIFS survivors in their series had significant scarring and sinus obstruction on long-term follow-up, with some patients experiencing complications or recurrence more than 1 year after initial surgery.[254] Table 38 summarizes evidence surrounding the use of bedside endoscopy for surveillance of AIFS.

Aggregate Grade of Evidence: D (Level 3: 1 study; Level 4: 2 studies; Level 5: 1 study).

14.2 | Repeat/serial imaging

There is a paucity of information on appropriate follow-up imaging for AIFS patients after initial treatment. Although non-contrast CT is often utilized in the initial diagnostic workup to evaluate bony erosion or evidence of soft tissue extension,[174] some studies have shown MRI with contrast has better sensitivity and specificity for AIFS.[99] Kim et al. demonstrated that evidence of loss of contrast enhancement on postoperative MRI within 4 weeks of surgery was associated with poor prognosis.[99] Given the risk for long-term sequelae of aggressive surgical debridement to treat AIFS, Monroe et al. recommended that imaging at 6 to 12 months during follow-up may be warranted.[41] Table 39 summarizes evidence surrounding the use of serial imaging for AIFS surveillance.

Aggregate Grade of Evidence: D (Level 4: 2 studies; Level 5: 1 study).

15 | DISCUSSION

There are multiple modalities available to the clinician for diagnosis of AIFS, including utilizing clinical signs and symptoms, endoscopy, biopsy, laboratory testing such as microbiology and histopathology, and imaging. As AIFS is associated with a high mortality rate, prompt and accurate diagnosis is paramount to appropriate management. Herein, a multidisciplinary consortium has reviewed the current literature regarding diagnosis of AIFS and provided recommendations based on benefits, risks, and costs that can be assimilated into clinical practice.

The first and foremost step in the diagnosis of AIFS is in recognizing the clinical signs and symptoms that would prompt further workup. There is currently sparse evidence on the utility of various symptoms for diagnosis of AIFS given the heterogeneous presentations. Specifically, there were no studies that identified sensitivity, specificity, or predictive value of AIFS symptoms, but studies did report fever, facial swelling, facial pain, and nasal congestion as common symptoms, and ophthalmoplegia, vision loss, and proptosis as common signs. Other studies assessed the prevalence of various constitutional, sinonasal, otolaryngologic, cranial nerve, and ophthalmologic manifestations of AIFS as described previously with each sign and symptom having widely varying prevalence depending on the study. With regard to timing and acuity, AIFS is described as having a duration of symptoms progressing in less than 4 weeks, with high mortality rates within this time-frame.[27,49,51,59,54]

Endoscopy is a common diagnostic procedure used in the workup of AIFS when there is clinical concern. Endoscopic findings have been shown to be highly specific in the diagnosis of AIFS, with mucosal edema, discoloration, ulceration, necrosis, and fungal elements being common findings. Although repeat endoscopic examination after debridement has been shown to be beneficial in management, with one study showing 40% of the patients who underwent a debridement required additional debridement, there is currently sparse literature on the timing, duration, and frequency of routine surveillance nasal endoscopy for those at risk of AIFS.[58] Although a positive endoscopy can aid in diagnosis of AIFS, a negative exam cannot exclude AIFS because mucosal changes may indicate a later stage disease, especially in undissected mucosa where deeper tissues may be infected, and due to the low sensitivity of the exam (49% to 75%).[7,19,38,58,63,85,86] As endoscopy is a relatively low-risk procedure that can be performed at bedside and has a high specificity, it is recommended as part of the first-line assessment when there is clinical suspicion for AIFS. Generally, local anesthetics are avoided during the initial exam to evaluate mucosal sensitivity.

Adjunctive to nasal endoscopy is bedside biopsy, which can be done at the time of endoscopy. This can be done through frozen section analysis to assess for invasive fungal elements, with numerous reports describing the middle turbinate being a high sensitivity sampling site, especially if mucosal discoloration is present.[63,88,90] Risks to bedside biopsy, albeit rare, are bleeding in patients with comorbid conditions (e.g., thrombocytopenia) and treatment delay while awaiting histopathologic analysis, and should be considered in most patients given its utility in most cases.

TABLE 38 Bedside endoscopy for follow-up and surveillance.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Malleshappa[43]	2020	3	Prospective cohort	AIFS patients ($n = 51$)	1) Number of surgeries 2) Overall survival	Difference in outcomes with a single surgery vs. multiple surgeries was not significant. No association was found between stage of disease and outcome. The overall survival rate was 68.2%; 73.5% survival rate for diabetics alone.
Otto[254]	2006	4	Case series	AIFS patients ($n = 13$)	1) Major complications 2) Minor complications (e.g., CRS)	Major complications on follow-up included complicated ARS with vision loss, chronic osteomyelitis of skull base and orbit, and recurrent AIFS. Minor complications in 46% due to chronic bacterial rhinosinusitis. Sixty-two percent of patients had sinus complications after clearance of AIFS and recovery of immune function on long-term follow-up.
Gillespie[89]	1998	4	Case series	AIFS patients ($n = 25$)	1) Disease-specific and overall mortality	Disease-specific mortality was 36% and overall mortality was 60%. Survivors had complete resection compared to nonsurvivors (90% vs. 0%) and were more likely to respond to G-CSF.
Fung[174]	2019	5	Expert opinion	N/A	1) Approach for diagnosis and management of AIFS	Three pillars in the treatment of invasive AIFS: (1) urgent surgical debridement; (2) antifungal therapy; and (3) reversal of immunosuppression. A "second look" surgery 1–2 weeks later in clinic or the operating room after initial surgery may be helpful to facilitate additional resection of concerning tissue or debridement of obstructing crusts or debris. Repeat imaging with CT scan is performed at short intervals only if there is a plan to return to the operating room for additional resection of tissue or if the patient's clinical picture is not improving.

TABLE 39 Serial imaging.

Study (first author)	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kim[99]	2015	4	Retrospective cohort	AIFS patients ($n = 21$)	1) Disease-specific survival 2) Presence of loss of contrast-enhancing lesions	Postoperative extrasinonasal loss of contrast enhancement lesions were found in all nonsurvivors but not in survivors. Remission of hematologic diseases at the time of AIFS diagnosis and glucose control in diabetic patients were significantly associated with AIFS-specific survival.
Monroe[41]	2013	4	Case series	AIFS patients ($n = 29$)	1) Disease-specific survival 2) Overall survival	Disease-specific survival was 57%; 6-month overall survival was 17%. Both intracranial and ethmoid sinus involvement were significantly linked with short-term disease-related mortality. Intracranial involvement and cranial neuropathy at presentation were significantly associated with shortened overall survival. Surviving patients were at risk for major long-term sinonasal complications.
Fung[174]	2019	5	Expert opinion	Not applicable	1) Approach for diagnosis and management of AIFS	Three pillars in the treatment of invasive AIFS: (1) urgent surgical debridement, (2) antifungal therapy, and (3) reversal of immunosuppression. A "second-look" surgery 1–2 weeks later in clinic or the operating room after initial surgery may be helpful to facilitate additional resection of concerning tissue or debridement of obstructing crusts or debris. Repeat imaging with CT scan is performed at short intervals only if there is a plan to return to the operating room for additional resection of tissue or if the patient's clinical picture is not improving.

FNAB has also been described for the workup of AIFS, with an apparently favorable safety profile. It is important to note that, with either tissue sampling method, the mere presence of fungal hyphae does not exclude or confirm angioinvasive disease.

As with many other disease processes, CT plays a vital role as a noninvasive diagnostic test for AIFS. In a study by Middlebrooks et al., a CT-based predictive tool was designed utilizing bony dehiscence, septal ulceration, and involvement of the periantral fat, orbit, pterygopalatine fossa, nasolacrimal duct, and lacrimal sac, with the presence of any of these features conferring a high sensitivity (95%), specificity (86%), PPV (87%), and NPV (95%) for AIFS.[95] The study was one of the first predictive tools in CT as others studied the presence of CT findings in patients with AIFS but did not explore in detail the diagnostic utility of each finding.

Although associated with higher costs, MRI plays an important role in assessment of soft tissue involvement of patients with suspected AIFS when compared with CT. Studies have described the "black turbinate sign" with LoCE as corresponding to angioinvasive mucosal infarction being highly sensitive and seemingly specific for AIFS.[19,96] Lagos et al. further described the presence of extrasinus and orbital extension as MRI findings that are highly associated with AIFS.[19] However, one study did describe the presence of LoCE in immunocompetent patients without AIFS, cautioning the use of LoCE as an indicator for immunocompetent patients.[97] LoCE as a prognostic indicator has been assessed by numerous studies, and is associated with poor prognosis in those with AIFS.[98–101] As such, the presence of LoCE on MRI should raise clinical suspicion and, in the properly selected patient, be considered for surgical debridement given that LoCE likely signifies tissue necrosis. In comparing CT and MRI, studies have shown that MRI has better sensitivity than CT, but similar specificity, PPV, NPV, and accuracy for diagnosis of AIFS. The American College of Radiology Appropriateness Criteria Sinonasal Disease was revised in 2017 to state that both MRI with and without contrast and non-contrast CT are "usually appropriate" tests.[103] Given the high accuracy and noninvasiveness of each study and minimal risk, the evidence supports the use of both CT and contrast-enhanced MRI (if not prohibiting timely intervention), as both play a complementary role in diagnosis.

Tissue culture and sensitivities provide important information on planning treatment of AIFS based on organism. Tissue fungal culture from operatively collected tissue has been shown to have the highest yield.[7,17,28,31,33,57,60–65] In addition, direct microscopy of the tissue specimens also allows for detection of fungal elements, but it may not allow for precise identification of organism and susceptibilities. PCR has also been shown to be an efficient adjunct diagnostic tool for AIFS. It allows for more expedient results and can be used in support of traditional techniques and will likely play an increasing role in diagnosis.[60]

Current data on non-microbiology laboratory studies such as leukocyte count and ANC, when used alone, have been shown to be limited in prognostic utility because there is no currently accepted level or range that can be associated with diagnosis. It has been shown that improved glycemic control with lower serum glucose and HbA1C is associated with improved survival in patients with AIFS.[4,5] Thus, tight glycemic control is recommended in patients with suspected AIFS.

In addition, frozen sections have been studied in the setting of diagnosis of AIFS, showing high sensitivity and specificity, with evidence that evaluation of multiple specimens from a single patient can increase diagnostic accuracy.[104] Although the use of intraoperative frozen specimens may extend operative time, the associated high specificity and PPV may validate its use to improve surgical clearance. On the choice of staining technique, multiple studies have validated the use of PASF-fs over H&E-fs given its higher sensitivity. However, it is also important to note that intraoperative frozen sections are not perfect—Gonzales et al. described a 15% overall error rate of frozen section samples in AIFS, with the majority of errors being interpretive.

For management of AIFS, there are many treatment options that clinicians may employ, including surgery, medical therapy, reversal of immunosuppression, and various modalities to address orbital involvement. Herein, this multidisciplinary, multicenter consortium reviewed the current literature regarding management of AIFS and provided recommendations based on benefits, risks, alternatives, and costs that can inform clinical practice.

Some of the best evidence on management of AIFS to date surrounds surgical debridement of infected/necrotic tissue. It has been consistently reported in the literature that surgery, as well as surgery in conjunction with medical therapy, improves survival in patients with AIFS compared with medical therapy alone.[4,35,45,54,68,120,121] With the data available, surgical debridement of infected/necrotic tissue for patients with AIFS is of critical importance, with upfront discussion of goals of care to determine extent of surgery and manage prognostic expectations. As AIFS has an aggressive disease course, it has traditionally been thought that early and timely surgery improves outcomes. Although most of the literature supports this statement, there are studies showing no difference in outcomes between urgent treatment and nonurgent treatment, and even one study showing improved outcomes with delayed treatment.[20,23,35,45,48,51,54,121–126] As such, optimal time to treatment remains unclear, as each study had

different time-points for "early" intervention, ranging from 4 to 16 days.

Although guidelines for extent of initial surgical resection have not been established, studies have shown that complete removal of tissue through radical resection improves survival rates compared with limited resection. With regard to surgical approaches, extended surgical approaches may comprehensively manage the affected surgical areas and prevent disease progression and recurrence.[38,121,129,133–136] We recommend extended endoscopic surgical approaches whenever conventional techniques are not sufficient, but surgeons must appreciate the unique risks associated with these extended approaches. In cases not amenable to complete endoscopic resection, open maxillectomy has shown variable survival outcomes, although this is likely confounded by presenting extent of disease.[137–141] Open approaches, which may be rather invasive and are thus associated with additional morbidity, aesthetic deformity, and residual functional defects, must be weighted with the patient's overall health status and aligned with goals of care. Intracranial involvement is associated with poor prognosis overall and there is limited evidence suggesting benefit in resecting intracranial disease, yet it represents an option and requires counseling patients about its associated risks and potential morbidity.[226,227,229]

As for surgical approach, there is currently no consensus on whether open, endoscopic, or combined approaches confer survival differences.[4,20,47,133] Given the evidence, we recommend endoscopic resection whenever possible and consideration for combined or open surgery in advanced cases not amenable to endoscopic resection. With AIFS having high potential for progression and recurrence, multiple debridements are common with reports that total number of surgeries ranges from one to seven in various series.[21,33,36,127,145,146] However, there is conflicting evidence on the impact of multiple surgeries on survival, and return to surgery timing has not been reported.[21,63,145,147] As such, we recommend the use of postoperative clinical exams, follow-up imaging, endoscopy, and surgical margins to guide the need for repeated surgical intervention when clinically indicated.

Complementary to surgical debridement is systemic antifungal therapy, where empiric therapy with amphotericin B is recommended once suspicion for AIFS is heightened. One study showed that, in cases of mucormycosis, delays exceeding 6 days before initiation of antifungal treatment resulted in a twofold increase in mortality at 12 weeks.[66] Current guidelines recommend use of the liposomal formulation of amphotericin B as it has broad coverage for both *Mucorales* and aspergillosis, and reduces risk of renal injury when compared with conventional preparations.[167,174,175]

Azoles also play a role in AIFS management. In the case of confirmed *Aspergillus*, the recommended first-line therapy is voriconazole, with one randomized controlled trial showing improved outcomes vs. amphotericin B. However, these data are mostly from patients with invasive pulmonary aspergillosis and only 25 of the 277 patients had AIFS.[67] There are currently no data comparing voriconazole to isuvaconazole or posaconazole for patients specifically with AIFS, but two trials showed similar outcomes with improved side-effect profiles in those with invasive aspergillosis.[176,177] In cases of azole resistance, amphotericin B is the recommended monotherapy, with a prospective study showing a response rate of 50% with use of liposomal amphotericin B in patients with invasive aspergillosis.[178] Caspofungin has also been described for use in combination therapy for *Aspergillus* AIFS, with some evidence suggesting that it is safe and effective.[179] Combination antifungal therapy is not routinely recommended and there is mixed evidence regarding its efficacy in severe cases of refractory *Aspergillus* AIFS.[3,56,68,84,105,149,180] Because *Mucorales* have innate resistance to voriconazole, guidelines recommend liposomal amphotericin B as first-line treatment, with dose increases for CNS involvement.[175,178] Topical antifungals for AIFS have not been well studied in the literature, with only low-level evidence showing no success in local disease control or survival associated with topical amphotericin B treatment.[255] As such, no recommendation can be given on the use of topical antifungals for treatment of AIFS.

There is currently limited evidence that defines duration of medical therapy for AIFS, with most studies indicating treatment until disease control (defined as resolution of all clinical and radiologic abnormalities), treatment intolerance, or death. Factors that influence treatment time include disease extension, smoking status, absence of a rhinologist on the treatment team, low absolute neutrophil count, hematologic malignancy, recent chemotherapy, and delayed time to surgery.[20,27,221,196,233]

Orbital involvement in AIFS has been reported to occur in at least half of cases and is considered a risk factor for poor overall survival.[4,57,155,173,217,218] In patients with orbital involvement, there have been studies on the use of retrobulbar antifungals, orbitotomy for debridement, and orbital exenteration. TRAMB injection and orbitotomy with amphotericin B irrigation has been described in the literature as an adjunct to surgical debridement. Ashraf et al. demonstrated a decreased relative risk of orbital exenteration in patients who underwent TRAMB, but no mortality benefit.[211] However, another study, by Arreenich et al., showed no significant difference in orbital exenteration or overall survival with TRAMB. As such, further studies must be done to validate the use of TRAMB and determine the optimal treatment paradigm. Orbital

exenteration has also been reported in the literature to have variable efficacy, with some studies showing no significant improvement in survival[4,57,147,165,216] and others demonstrating survival benefit.[217,220] Last, one study showed that, although orbital exenteration did not improve overall survival, it did increase mean time of symptom onset to death.[147] In conclusion, orbital exenteration remains an option for AIFS patients with an involved nonfunctional eye, but without clear survival benefit.

As AIFS is a disease primarily of the immunocompromised, reversing immunosuppression is an important component of treatment. Diabetes, as a source of immunosuppression, is present in up to half of patients with AIFS, and has been reported to decrease overall survival in AIFS,[39,48,57,105,144,210,230] with comparatively worse outcomes compared with other sources of immunosuppression.[56,83] However, several cohort studies reported no significant association or even improvements in survival with diabetic AIFS, attributing this to the fact that immunosuppression in diabetes is more readily reversible than other causes.[56,48,68,83,105,133] Although there is no consensus on the impact of diabetes in mortality in AIFS, tight glycemic control and rapid reversal of hyperglycemic states are critical for optimizing treatment in affected AIFS patients.

Several modalities for actively reversing immunosuppression in leukopenic patients have been described in the setting of AIFS, including leukocyte infusions, G-CSF, and immunomodulating agents. Neutropenia has been reported to be a risk factor in developing AIFS and is a negative prognosticator for survival.[68,84,231] Accordingly, studies have shown that recovery of absolute neutrophil count has been associated with survival in AIFS patients.[233,234] As such, leukocyte infusions have been hypothesized to increase survival; however, the data are limited, with only a few studies showing containment of infection after granulocyte infusion and one study showing no significant improvement in overall survival.[41,83,231] G-CSF has also been described in the literature for increasing neutrophil counts, but the data are mixed and limited on use in AIFS. There are few cohort studies showing promising prognostic signs and one multi-institutional review showing a 70% reduction in 1-month mortality, but no difference in 3-month mortality.[83,89,233] However, there are multiple studies that showed no improvements in short-term survival or overall survival with G-CSF treatment, necessitating further investigation to assess efficacy.[6,18,41] There are other immunomodulating agents that have been described in the literature, such as interferon-γ, anti-*Aspergillus* T cell transfer, and D-chimeric antigen receptor T cells, but these agents are largely in the exploratory stage.[238–243] To date, the evidence for active leukocyte stimulation for AIFS is limited.

Another immunosuppressive state that has been studied in the context of AIFS is posttransplantation. Patients who undergo SCT or BMT have periods of prolonged neutropenia, but studies have shown that neither BMT nor SCT has significant associations with AIFS.[48,68] For solid-organ transplantation, cohort studies have shown no significant association with AIFS.[56,155] The literature has also implicated COVID-19 as a source of immunosuppression in AIFS, but the evidence remains very new, and there have been suggestions that unfavorable outcomes are due to immunosuppressive corticosteroid use in the setting of COVID-19.[29,153,216,217,248–249,256]

As AIFS outcomes are guarded and estimates for survival are between 40% and 80%, development of long-term follow-up and screening protocols are paramount.[4,5,18,23,41,83,250] Currently, no consensus exists in this area. Endoscopy has been recommended weekly or biweekly until remucosalization, confirmation of no progressive disease, and recovery of normal sinus physiology.[21,99,174] There is also currently a paucity of information regarding imaging for AIFS patients after treatment, but, given the long-term sequelae of AIFS, there have been recommendations of imaging at 6 to 12 months for follow-up.[41] Ultimately, a critical need in AIFS research is utilizing criteria for endoscopic or radiographic resolution of disease to guide duration of medical therapy, thereby establishing protocols (e.g., akin to cancer surveillance).

This evidence-based review has utilized the best available, up-to-date evidence on the principles and recommendations surrounding the diagnosis, prognosis, and management of AIFS, and leveraged the expertise of a multidisciplinary group of specialists who treat this condition. Nonetheless, there is currently a lack of consensus owing to low-level evidence in many areas. Future areas of investigation include, but are not limited to:

- Recommended timing for surgical debridement from time of presentation to medical facilities.
- Optimal extent of surgery, including the value of being aggressive with orbital and/or intracranial debridement.
- Optimal duration and dose of antifungal therapy, and novel/alternative means to mitigate side effects related to treatment.
- Quantifiable endpoints for adequate reversal of immunosuppression.
- Understanding whether increased neutrophil count translates into intact immune function.
- Prognosis and management strategies for COVID-19–related AIFS.
- Long-term follow-up and surveillance protocol after adequate AIFS treatment, and guiding duration of medical therapy based on this.

- The prognostic importance of the rate of evolution of signs and symptoms.
- Pathophysiologic mechanisms for tissue and vascular invasion by offending fungal organisms.
- Underlying differences in biologic behavior between different fungal organisms.
- Optimal sites of inspection in endoscopy and sites for bedside biopsy.
- Optimal timing of imaging, particularly in setting of disease progression (e.g., when should MRI be considered to rule out subclinical intracranial involvement?).
- The utility of frozen sections as it applies to extent of initial plan for surgical debridement.

16 | CONCLUSION

In this evidence-based review we have explored the different modalities used in the diagnosis, prognosis, and management of AIFS, and provided recommendations based on the current level of evidence. As AIFS is an aggressive disease, prompt diagnosis and treatment is paramount to decreasing mortality. Diagnosis of AIFS consists of clinical suspicion through signs and symptoms, endoscopy and biopsy, imaging, culture and laboratory tests, and pathology. All of these play an important role in diagnosis, as invasive disease is hard to determine with a singular test. Management of AIFS consists of surgery, medical therapy with antifungals, reversing immunosuppression, and management of orbital/intracranial extension. Although some modalities have been more well-studied and widely employed, each management option plays an important role in treatment. Despite numerous attempts to determine protocols across various subspecialities, the current level of evidence for AIFS remains relatively poor and necessitates further research.

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REFERENCES

1. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. 2021;11(3):213-739. doi:10.1002/alr.22741
2. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinol J*. 2020;0(0):1-464. doi:10.4193/Rhin20.600
3. Candoni A, Klimko N, Busca A, et al. Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. *Mycoses*. 2019;62(3):252-260. doi:10.1111/myc.12884
4. Turner JH, Soudry E, Nayak JV, Hwang PH. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence: survival outcomes in invasive fungal sinusitis. *Laryngoscope*. 2013;123(5):1112-1118. doi:10.1002/lary.23912
5. Wandell GM, Miller C, Rathor A, et al. A multi-institutional review of outcomes in biopsy-proven acute invasive fungal sinusitis: outcomes with IFS. *Int Forum Allergy Rhinol*. 2018;8(12):1459-1468. doi:10.1002/alr.22172
6. Roxbury CR, Smith DF, Higgins TS, et al. Complete surgical resection and short-term survival in acute invasive fungal rshinosinusitis. *Am J Rhinol Allergy*. 2017;31(2):109-116. doi:10.2500/ajra.2017.31.4420
7. Davoudi S, Kumar VA, Jiang Y, Kupferman M, Kontoyiannis DP. Invasive mould sinusitis in patients with haematological malignancies: a 10 year single-centre study. *J Antimicrob Chemother*. 2015;70(10):2899-2905. doi:10.1093/jac/dkv198
8. Raizada N, Jyotsna VP, Kandasamy D, Xess I, Thakar A, Tandon N. Invasive fungal rhinosinusitis in patients with diabetes. *J Infect Dev Ctries*. 2018;12(09):787-793. doi:10.3855/jidc.9699
9. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020;71(6):1367-1376. doi:10.1093/cid/ciz1008
10. Ruhnke M, Cornely OA, Schmidt-Hieber M, et al. Treatment of invasive fungal diseases in cancer patients—Revised 2019 Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Mycoses*. 2020;63(7):653-682. doi:10.1111/myc.13082
11. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1(6):431-437. doi:10.1002/alr.20095

12. Oxford Centre for Evidence-based Medicine (CEBM) - Levels of Evidence. Published online 2011. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
13. Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874-877. doi:10.1542/peds.2004-1260
14. Cohn SM, Pokala HR, Siegel JD, et al. Application of a standardized screening protocol for diagnosis of invasive mold infections in children with hematologic malignancies. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2016;24(12):5025-5033. doi:10.1007/s00520-016–3367-z
15. Green KK, Barham HP, Allen GC, Chan KH. Prognostic factors in the outcome of invasive fungal sinusitis in a pediatric population. *Pediatr Infect Dis J*. 2016;35(4):384-386. doi:10.1097/INF.0000000000001015
16. Zhang H, Jiang N, Lin X, Wanggou S, Olson JJ, Li X. Invasive sphenoid sinus aspergillosis mimicking sellar tumor: a report of 4 cases and systematic literature review. *Chin Neurosurg J*. 2020;6(1):10. doi:10.1186/s41016-020-00187-0
17. Hua MW, Wu CY, Jiang RS, Chang CY, Liang KL. Validate the classification of fungal rhinosinusitis: a retrospective analysis of 162 patients at a single institution. *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg*. 2019;44(6):1131-1137. doi:10.1111/coa.13413
18. Smith A, Thimmappa V, Shepherd B, Ray M, Sheyn A, Thompson J. Invasive fungal sinusitis in the pediatric population: systematic review with quantitative synthesis of the literature. *Int J Pediatr Otorhinolaryngol*. 2016;90:231-235. doi:10.1016/j.ijporl.2016.09.019
19. Lagos AE, García-Huidobro FG, Sepúlveda V, Cruz JP, González C, Callejas CA. Determination of variables for a more accurate diagnostic approach in suspected acute invasive fungal rhinosinusitis: a non-concurrent cohort study. *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg*. 2021;46(4):775-781. doi:10.1111/coa.13734
20. Alejandro A, de la Torre González C, Edgar M, Perla V. Factors associated with all-cause mortality in pediatric invasive fungal rhinosinusitis. *Int J Pediatr Otorhinolaryngol*. 2020;129:109734. doi:10.1016/j.ijporl.2019.109734
21. Malleshappa V, Rupa V, Varghese L, Kurien R. Avoiding repeated surgery in patients with acute invasive fungal sinusitis. *Eur Arch Otorhinolaryngol*. 2020;277(6):1667-1674. doi:10.1007/s00405-020-05879-y
22. D'Andrea MR, Gill CM, Umphlett M, et al. Benefit of Endoscopic Surgery in the Management of Acute Invasive Skull Base Fungal Rhinosinusitis. *J Neurol Surg Part B Skull Base*. 2021;82(S 03):e330-e334. doi:10.1055/s-0040-1701681
23. Fernandez IJ, Crocetta FM, Dematté M, et al. Acute Invasive Fungal Rhinosinusitis in Immunocompromised Patients: role of an Early Diagnosis. *Otolaryngol Neck Surg*. 2018;159(2):386-393. doi:10.1177/0194599818765744
24. DelGaudio JM, Clemson LA. An early detection protocol for invasive fungal sinusitis in neutropenic patients successfully reduces extent of disease at presentation and long term morbidity. *The Laryngoscope*. 2009;119(1):180-183. doi:10.1002/lary.20014
25. Ingley AP, Parikh SL, DelGaudio JM. Orbital and Cranial Nerve Presentations and Sequelae are Hallmarks of Invasive Fungal Sinusitis caused by Mucor in Contrast to Aspergillus. *Am J Rhinol*. 2008;22(2):155-158. doi:10.2500/ajr.2008.22.3141
26. Abdollahi A, shokohi T, et al. Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis: a retrospective analysis. *Curr Med Mycol*. 2016;2(4):15-23. doi:10.18869/acadpub.cmm.2.4.15
27. Gardner JR, Hunter CJ, Vickers D, King D, Kanaan A. Perioperative Indicators of Prognosis in Acute Invasive Fungal Sinusitis. *OTO Open*. 2021;5(1):2473974×2110025. doi:10.1177/2473974%D7;211002547
28. Gür H, İsmi O, Vayısoğlu Y, et al. Clinical and surgical factors affecting the prognosis and survival rates in patients with mucormycosis. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg*. 2021. doi:10.1007/s00405-021-06910-6. Published online June 1.
29. Sebastian SK, Kumar VB, Gupta M, Sharma Y. Covid Assossiated Invasive Fungal Sinusitis. *Indian J Otolaryngol Head Neck Surg*. 2021. doi:10.1007/s12070-021-02471-6. Published online February 25.
30. Coutel M, Duprez T, Huart C, Wacheul E, Boschi A. Invasive Fungal Sinusitis with Ophthalmological Complications: case Series and Review of the Literature. *Neuro-Ophthalmol*. 2021;45(3):193-204. doi:10.1080/01658107.2020.1779315
31. Wei H, Li Y, Han D, et al. The values of (1,3)-β-D-glucan and galactomannan in cases of invasive fungal rhinosinusitis. *Am J Otolaryngol*. 2021;42(2):102871. doi:10.1016/j.amjoto.2020.102871
32. Fadda GL, Martino F, Andreani G, et al. Definition and management of invasive fungal rhinosinusitis: a single-centre retrospective study. *Acta Otorhinolaryngol Ital*. 2021;41(1):43-50. doi:10.14639/0392-100X-N0848
33. Shanbag R, Rajan NR, Kumar A. Acute invasive fungal rhinosinusitis: our 2 year experience and outcome analysis. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg*. 2019;276(4):1081-1087. doi:10.1007/s00405-019-05288-w
34. Cho SW, Lee WW, Ma D, et al. Orbital Apex Lesions: a Diagnostic and Therapeutic Challenge. *J Neurol Surg Part B Skull Base*. 2018;79(04):386-393. doi:10.1055/s-0037-1612616
35. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis-has anything changed in the past 20 years? *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg*. 2018;43(6):1454-1464. doi:10.1111/coa.13175
36. Ergun O, Tahir E, Kuscu O, Ozgen B, Yilmaz T. Acute Invasive Fungal Rhinosinusitis: presentation of 19 Cases, Review of the Literature, and a New Classification System. *J Oral Maxillofac Surg*. 2017;75(4):767.e1-767.e9. doi:10.1016/j.joms.2016.11.004
37. Bakhshaee M, Bojdi A, Allahyari A, et al. Acute invasive fungal rhinosinusitis: our experience with 18 cases. *Eur Arch Otorhinolaryngol*. 2016;273(12):4281-4287. doi:10.1007/s00405-016–4109-z
38. Payne SJ, Mitzner R, Kunchala S, Roland L, McGinn JD. Acute Invasive Fungal Rhinosinusitis: a 15-Year Experience with 41 Patients. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2016;154(4):759-764. doi:10.1177/0194599815627786

39. Cho HJ, Jang MS, Hong SD, Chung SK, Kim HY, Dhong HJ. Prognostic Factors for Survival in Patients with Acute Invasive Fungal Rhinosinusitis. *Am J Rhinol Allergy*. 2015;29(1):48-53. doi:10.2500/ajra.2015.29.4115
40. Lee DY, Chung EL, Guend H, Whelan RL, Wedderburn RV, Rose KM. Predictors of Mortality After Emergency Colectomy for Clostridium Difficile Colitis: an Analysis of ACS-NSQIP. *Ann Surg*. 2014;259(1):148-156. doi:10.1097/SLA.0b013e31828a8eba
41. Monroe MM, McLean M, Sautter N, et al. Invasive Fungal Rhinosinusitis: a 15-Year Experience With 29 Patients. *Laryngoscope*. 2013;123(7):1583-1587. doi:10.1002/lary.23978
42. Arora V, Nagarkar NM, Dass A, Malhotra A. Invasive Rhino-Orbital Aspergillosis. *Indian J Otolaryngol Head Neck Surg*. 2011;63(4):325-329. doi:10.1007/s12070-011–0240–8
43. Takahashi H, Hinohira Y, Hato N, et al. Clinical features and outcomes of four patients with invasive fungal sinusitis. *Auris Nasus Larynx*. 2011;38(2):289-294. doi:10.1016/j.anl.2010.08.003
44. Süslü AE, Öğretmenoğlu O, Süslü N, Yücel ÖT, Önerci TM. Acute invasive fungal rhinosinusitis: our experience with 19 patients. *Eur Arch Otorhinolaryngol*. 2009;266(1):77-82. doi:10.1007/s00405-008–0694–9
45. Bhansali A, Bhadada S, Sharma A, et al. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. *Postgrad Med J*. 2004;80(949):670-674. doi:10.1136/pgmj.2003.016030
46. Anselmo-Lima WT, Lopes RP, Valera FCP, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. *Rhinology*. 2004;42(3):141-144.
47. Sohail MA, Al Khabori M, Hyder J, Verma A. Acute fulminant fungal sinusitis: clinical presentation, radiological findings and treatment. *Acta Trop*. 2001;80(2):177-185. doi:10.1016/S0001-706X(01)00174-7
48. Kennedy CA, Adams GL, Neglia JP, Giebink GS. Impact of surgical treatment on paranasal fungal infections in bone marrow transplant patients. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 1997;116(6 Pt 1):610-616. doi:10.1016/S0194-59989770236-5
49. Iwen PC, Rupp ME, Hinrichs SH. Invasive mold sinusitis: 17 cases in immunocompromised patients and review of the literature. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1997;24(6):1178-1184. doi:10.1086/513662
50. Al-Bhlal LA. Fungal Infection of the Nasal Cavity and Paranasal Sinuses: review of 26 Cases. *Ann Saudi Med*. 1996;16(6):615-621. doi:10.5144/0256–4947.1996.615
51. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol*. 1994;39(1):3-22. doi:10.1016/s0039-6257(05)80041-4
52. Drakos PE, Nagler A, Or R, et al. Invasive fungal sinusitis in patients undergoing bone marrow transplantation. *Bone Marrow Transplant*. 1993;12(3):203-208.
53. Talbot GH, Huang A, Provencher M. Invasive Aspergillus Rhinosinusitis in Patients with Acute Leukemia. *Clin Infect Dis*. 1991;13(2):219-232. doi:10.1093/clinids/13.2.219
54. Blitzer A, Lawson W, Meyers BR, Biller HF. Patient survival factors in paranasal sinus mucormycosis. *Laryngoscope*. 1980;90(4):635-648. doi:10.1288/00005537-198004000-00010
55. Lee DH, Yoon TM, Lee JK, Joo YE, Park KH, Lim SC. Invasive Fungal Sinusitis of the Sphenoid Sinus. *Clin Exp Otorhinolaryngol*. 2014;7(3):181. doi:10.3342/ceo.2014.7.3.181
56. Vengerovich G, Echanique KA, Park KW, et al. Retrospective Analysis of Patients With Acute Invasive Fungal Rhinosinusitis in a Single Tertiary Academic Medical Center: a 10-Year Experience. *Am J Rhinol Allergy*. 2020;34(3):324-330. doi:10.1177/1945892419896233
57. Hirabayashi KE, Idowu OO, Kalin-Hajdu E, et al. Invasive Fungal Sinusitis: risk Factors for Visual Acuity Outcomes and Mortality. *Ophthal Plast Reconstr Surg*. 2019;35(6):535-542. doi:10.1097/IOP.0000000000001357
58. Mulvey CL, Rizzi MD, Buzi A. Predictive ability of bedside nasal endoscopy to diagnose invasive fungal sinusitis in a pediatric population. *Int J Pediatr Otorhinolaryngol*. 2018;115:82-88. doi:10.1016/j.ijporl.2018.09.019
59. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *The Laryngoscope*. 2009;119(9):1809-1818. doi:10.1002/lary.20520
60. Lieberman JA, Bryan A, Mays JA, et al. High Clinical Impact of Broad-Range Fungal PCR in Suspected Fungal Sinusitis. *J Clin Microbiol*. 2021;59(11):e0095521. doi:10.1128/JCM.00955-21
61. Badiee P, Moghadami M, Rozbehani H. Comparing immunological and molecular tests with conventional methods in diagnosis of acute invasive fungal rhinosinusitis. *J Infect Dev Ctries*. 2016;10(1):90-95. doi:10.3855/jidc.6411
62. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2013;57(4):e22-e121. doi:10.1093/cid/cit278
63. Silveira MLC, Anselmo-Lima WT, Faria FM, et al. Impact of early detection of acute invasive fungal rhinosinusitis in immunocompromised patients. *BMC Infect Dis*. 2019;19(1):310. doi:10.1186/s12879-019–3938-y
64. Raiesi O, Hashemi SJ, Mohammadi Ardehali M, et al. Molecular identification and clinical features of fungal rhinosinusitis: a 3-year experience with 108 patients. *Microb Pathog*. 2021;158:105018. doi:10.1016/j.micpath.2021.105018
65. Montone KT, Livolsi VA, Feldman MD, et al. Fungal rhinosinusitis: a retrospective microbiologic and pathologic review of 400 patients at a single university medical center. *Int J Otolaryngol*. 2012;2012:684835. doi:10.1155/2012/684835
66. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying Amphotericin B–Based Frontline Therapy Significantly Increases Mortality among Patients with Hematologic Malignancy Who Have Zygomycosis. *Clin Infect Dis*. 2008;47(4):503-509. doi:10.1086/590004
67. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. *N Engl J Med*. 2002;347(6):408-415. doi:10.1056/NEJMoa020191
68. Chen CY, Sheng WH, Cheng A, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. *BMC Infect Dis*. 2011;11:250. doi:10.1186/1471–2334-11-250

69. Sangoi AR, Rogers WM, Longacre TA, Montoya JG, Baron EJ, Banaei N. Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens: a ten-year retrospective review at a single institution. *Am J Clin Pathol*. 2009;131(3):364-375. doi:10.1309/AJCP99OOOZSNISCZ
70. Gomez CA, Budvytiene I, Zemek AJ, Banaei N. Performance of Targeted Fungal Sequencing for Culture-Independent Diagnosis of Invasive Fungal Disease. *Clin Infect Dis*. 2017;65(12):2035-2041. doi:10.1093/cid/cix728
71. Kerkhoff AD, Rutishauser RL, Miller S, Babik JM. Clinical Utility of Universal Broad-Range Polymerase Chain Reaction Amplicon Sequencing for Pathogen Identification: a Retrospective Cohort Study. *Clin Infect Dis*. 2020;71(6):1554-1557. doi:10.1093/cid/ciz1245
72. Cruciani M, Mengoli C, Barnes R, et al. Polymerase chain reaction blood tests for the diagnosis of invasive aspergillosis in immunocompromised people. *Cochrane Database Syst Rev*. 2019;9:CD009551. doi:10.1002/14651858.CD009551.pub4
73. Lass-Flörl C, Mutschlechner W, Aigner M, et al. Utility of PCR in Diagnosis of Invasive Fungal Infections: real-Life Data from a Multicenter Study. *J Clin Microbiol*. 2013;51(3):863-868. doi:10.1128/JCM.02965-12
74. Zhao Z, Li L, Wan Z, Chen W, Liu H, Li R. Simultaneous Detection and Identification of Aspergillus and Mucorales Species in Tissues Collected from Patients with Fungal Rhinosinusitis. *J Clin Microbiol*. 2011;49(4):1501-1507. doi:10.1128/JCM.02262-10
75. Theel ES, Doern CD. Point-Counterpoint: β- D -Glucan Testing Is Important for Diagnosis of Invasive Fungal Infections. *J Clin Microbiol*. 2013;51(11):3478-3483. doi:10.1128/JCM.01737-13
76. Metan G, Nedret Koc A, Ağkuş Ç, Kaynar LG, Alp E, Eser B. Can bacteraemia lead to false positive results in 1,3-beta-d-glucan test? Analysis of 83 bacteraemia episodes in high-risk patients for invasive fungal infections. *Rev Iberoam Micol*. 2012;29(3):169-171. doi:10.1016/j.riam.2011.07.003
77. Chang SW, Nam JS, Ha JG, et al. Detecting serum galactomannan to diagnose acute invasive Aspergillus sinusitis: a meta-analysis. *Eur Arch Otorhinolaryngol*. 2022;279(2):793-800. doi:10.1007/s00405-021-06857-8
78. Cho HJ, Hong SD, Kim HY, Chung SK, Dhong HJ. Clinical implications of serum galactomannan measurement in patients with acute invasive fungal rhinosinusitis. *Rhinol J*. 2016;54(4):336-341. doi:10.4193/Rhino15.186
79. Melancon CC, Lindsey J, Russell GB, Clinger JD. The role of galactomannan *Aspergillus* antigen in diagnosing acute invasive fungal sinusitis: galactomannan in diagnosis of AIFS. *Int Forum Allergy Rhinol*. 2019;9(1):60-66. doi:10.1002/alr.22225
80. Walter W, Bornhäuser M, Stölzel F, Zeidler A, Knoth H. In vitro detection of Candida and Aspergillus antigen in parenteral nutrition and fixed combinations of piperacillin-tazobactam. *Mycoses*. 2018;61(12):931-937. doi:10.1111/myc.12841
81. Chen CY, Sheng WH, Cheng A, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. *BMC Infect Dis*. 2011;11(1):250. doi:10.1186/1471–2334-11-250
82. Parasher AK, Lerner DK, Glicksman JT, Nabavizadeh SA, Palmer JN, Adappa ND. Clinical and Radiographic Characteristics of Sinonasal Posttransplant Lymphoproliferative Disorder and Invasive Fungal Sinusitis. *ORL*. 2019;81(5–6):294-303. doi:10.1159/000501938
83. Parikh SL, Venkatraman G, DelGaudio JM. Invasive fungal sinusitis: a 15-year review from a single institution. *Am J Rhinol*. 2004;18(2):75-81.
84. Gode S, Turhal G, Ozturk K, Aysel A, Midilli R, Karci B. Acute Invasive Fungal Rhinosinusitis: survival Analysis and the Prognostic Indicators. *Am J Rhinol Allergy*. 2015;29(6):e164-e169. doi:10.2500/ajra.2015.29.4245
85. Yin LX, Spillinger A, Lees KA, et al. An internally validated diagnostic tool for acute invasive fungal sinusitis. *Int Forum Allergy Rhinol*. 2021;11(1):65-74. doi:10.1002/alr.22635
86. Park AH, Muntz HR, Smith ME, Afify Z, Pysher T, Pavia A. Pediatric invasive fungal rhinosinusitis in immunocompromised children with cancer. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2005;133(3):411-416. doi:10.1016/j.otohns.2005.04.014
87. Abuzeid WM, Trott E, Jafari A, Moe KS, Humphreys IM. Is There a Role for Bedside Biopsy in the Evaluation of Acute Invasive Fungal Rhinosinusitis? *Laryngoscope*. 2021:lary.30002. doi:10.1002/lary.30002. Published online December 28.
88. Ghadiali MT, Deckard NA, Farooq U, Astor F, Robinson P, Casiano RR. Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2007;136(5):714-719. doi:10.1016/j.otohns.2007.01.002
89. Gillespie MB, O'Malley BW, Francis HW. An Approach to Fulminant Invasive Fungal Rhinosinusitis in the Immunocompromised Host. *Arch Otolaryngol Neck Surg*. 1998;124(5):520. doi:10.1001/archotol.124.5.520
90. Singhal N, Raghubanshi G, Handa U, Punia RPS, Singhal S. Fine needle aspiration cytology: a useful technique for diagnosis of invasive fungal rhinosinusitis. *Head Neck Pathol*. 2013;7(3):236-240. doi:10.1007/s12105-013–0434-3
91. Singh N, Siddaraju N, Kumar S, Muniraj F, Bakshi S, Gopalakrishnan S. Fine-needle aspiration biopsy as an initial diagnostic modality in a clinically unsuspected case of invasive maxillary fungal sinusitis: a case report. *Diagn Cytopathol*. 2010;38(4):290-293. doi:10.1002/dc.21216
92. Saah D, Sichel JY, Schwartz A, Nagler A, Eliashar R. CT assessment of bone marrow transplant patients with rhinocerebral aspergillosis. *Am J Otolaryngol*. 2002;23(6):328-331. doi:10.1053/ajot.2002.128040
93. DelGaudio JM, Swain RE, Kingdom TT, Muller S, Hudgins PA. Computed Tomographic Findings in Patients With Invasive Fungal Sinusitis. *Arch Otolaryngol Neck Surg*. 2003;129(2):236. doi:10.1001/archotol.129.2.236
94. Silverman CS, Mancuso AA. Periantral soft-tissue infiltration and its relevance to the early detection of invasive fungal sinusitis: cT and MR findings. *AJNR Am J Neuroradiol*. 1998;19(2):321-325.
95. Middlebrooks EH, Frost CJ, De Jesus RO, Massini TC, Schmalfuss IM, Mancuso AA. Acute Invasive Fungal Rhinosinusitis: a Comprehensive Update of CT Findings and Design of an Effective Diagnostic Imaging Model. *AJNR Am J Neuroradiol*. 2015;36(8):1529-1535. doi:10.3174/ajnr.A4298
96. Safder S, Carpenter JS, Roberts TD, Bailey N. The "Black Turbinate" sign: an early MR imaging finding of nasal mucormycosis. *AJNR Am J Neuroradiol*. 2010;31(4):771-774. doi:10.3174/ajnr.A1808

97. Han Q, Escott EJ. The Black Turbinate Sign, A Potential Diagnostic Pitfall: evaluation of the Normal Enhancement Patterns of the Nasal Turbinates. *AJNR Am J Neuroradiol*. 2019;40(5):855-861. doi:10.3174/ajnr.A6037
98. Seo J, Kim HJ, Chung SK, et al. Cervicofacial tissue infarction in patients with acute invasive fungal sinusitis: prevalence and characteristic MR imaging findings. *Neuroradiology*. 2013;55(4):467-473. doi:10.1007/s00234-013–1147–8
99. Kim JH, Kang BC, Lee JH, Jang YJ, Lee BJ, Chung YS. The prognostic value of gadolinium-enhanced magnetic resonance imaging in acute invasive fungal rhinosinusitis. *J Infect*. 2015;70(1):88-95. doi:10.1016/j.jinf.2014.07.027
100. Choi YR, Kim JH, Min HS, et al. Acute invasive fungal rhinosinusitis: mR imaging features and their impact on prognosis. *Neuroradiology*. 2018;60(7):715-723. doi:10.1007/s00234-018–2034-0
101. Nam SH, Chung YS, Choi YJ, Lee JH, Kim JH. Treatment outcomes in acute invasive fungal rhinosinusitis extending to the extrasinonasal area. *Sci Rep*. 2020;10(1):3688. doi:10.1038/s41598-020-60719-7
102. Groppo ER, El-Sayed IH, Aiken AH, Glastonbury CM. Computed tomography and magnetic resonance imaging characteristics of acute invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg*. 2011;137(10):1005-1010. doi:10.1001/archoto.2011.170
103. Expert Panel on Neurologic Imaging:, Kirsch CFE, Bykowski J, et al, Expert Panel on Neurologic Imaging. ACR Appropriateness Criteria® Sinonasal Disease. *J Am Coll Radiol JACR*. 2017;14(11S):S550-S559. doi:10.1016/j.jacr.2017.08.041
104. Kim DH, Kim SW, Hwang SH. Usefulness of intraoperative frozen section for diagnosing acute invasive fungal rhinosinusitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2021;11(9):1347-1354. doi:10.1002/alr.22797
105. Foshee J, Luminais C, Casey J, et al. An evaluation of invasive fungal sinusitis outcomes with subsite analysis and use of frozen section analysis: subsite analysis in invasive fungal sinusitis. *Int Forum Allergy Rhinol*. 2016;6(8):807-811. doi:10.1002/alr.21714
106. Hennessy M, McGinn J, White B, Payne S, Warrick JI, Crist H. Frozen Section as a Rapid and Accurate Method for Diagnosing Acute Invasive Fungal Rhinosinusitis. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2018;159(3):576-580. doi:10.1177/0194599818770615
107. Crist H, Hennessy M, Hodos J, et al. Acute Invasive Fungal Rhinosinusitis: frozen Section Histomorphology and Diagnosis with PAS Stain. *Head Neck Pathol*. 2019;13(3):318-326. doi:10.1007/s12105-018–0965–8
108. Gonzalez ML, Chen S, Mazaheri P, Schneider J, Chernock R. Acute Invasive Fungal Sinusitis: a 30-Year Review of Pathology Practice and Possible Utility of the DiffQuik® Stain. *Head Neck Pathol*. 2021;15(3):852-858. doi:10.1007/s12105-021-01295-8
109. Alkhateb R, Menon PD, Tariq H, Hackman S, Nazarullah A, Mais DD. Accuracy of Intraoperative Frozen Section in Detection of Acute Invasive Fungal Rhinosinusitis. *Arch Pathol Lab Med*. 2021;145(6):736-743. doi:10.5858/arpa.2019-0696-OA
110. Melancon CC, Clinger JD. The Use of Frozen Section in the Early Diagnosis of Acute Invasive Fungal Sinusitis. *Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2017;157(2):314-319. doi:10.1177/0194599817697279
111. Papagiannopoulos P, Lin DM, Al-Khudari S, et al. Utility of intraoperative frozen sections in surgical decision making for acute invasive fungal rhinosinusitis. *Int Forum Allergy Rhinol*. 2017;7(5):502-507. doi:10.1002/alr.21918
112. Taxy JB, El-Zayaty S, Langerman A. Acute fungal sinusitis: natural history and the role of frozen section. *Am J Clin Pathol*. 2009;132(1):86-93. doi:10.1309/AJCP9HTH9NRPMYCT
113. Hofman V, Castillo L, Bétis F, Guevara N, Gari-Toussaint M, Hofman P. Usefulness of frozen section in rhinocerebral mucormycosis diagnosis and management. *Pathology (Phila)*. 2003;35(3):212-216. doi:10.1080/0031302031000123173
114. Myoken Y, Sugata T, Katayama Y, Murayama SY. Prompt and definitive diagnosis of acute invasive Aspergillus rhinosinusitis in a patient with acute myeloid leukaemia using in situ hybridization: a case report. *Mycoses*. 2012;55(2):e23-26. doi:10.1111/j.1439-0507.2011.02077.x
115. Chaturantabut S, Kitkumtorn N, Mutirangura A, et al. Identification of pathogens causing invasive fungal rhinosinusitis in surgical biopsies using polymerase chain reaction. *J Laryngol Otol*. 2020;134(7):632-635. doi:10.1017/S0022215120001395
116. Huang YD, Yu HW, Xia SW, Kang ZH, He YS, Han DY. Expression of maspin in invasive fungal rhinosinusitis. *J Laryngol Otol*. 2017;131(2):150-154. doi:10.1017/S0022215116009890
117. Schuman TA, Nguyen JH, Yelverton JC, Almenara JA, Powers CN. The Sensitivity and Specificity of Touch Preparation for Rapid Diagnosis of Invasive Fungal Sinusitis: a Pilot Study. *Ear Nose Throat J*. 2021;100(1):55-59. doi:10.1177/0145561319840853
118. Piao YS, Zhang Y, Yang X, He CY, Liu HG. The use of MUC5B antibody in identifying the fungal type of fungal sinusitis. *Hum Pathol*. 2008;39(5):650-656. doi:10.1016/j.humpath.2007.07.017
119. Craig JR. Updates in management of acute invasive fungal rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg*. 2019;27(1):29-36. doi:10.1097/MOO.0000000000000507
120. Sun HY, Forrest G, Gupta KL, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. *Transplantation*. 2010;90(1):85-92. doi:10.1097/tp.0b013e3181dde8fc
121. Jung SH, Kim SW, Park CS, et al. Rhinocerebral Mucormycosis: consideration of prognostic factors and treatment modality. *Auris Nasus Larynx*. 2009;36(3):274-279. doi:10.1016/j.anl.2008.07.003
122. Piromchai P, Thanaviratananich S. Impact of Treatment Time on the Survival of Patients Suffering from Invasive Fungal Rhinosinusitis. *Clin Med Insights Ear Nose Throat*. 2014;7:CMENT.S18875. doi:10.4137/CMENT.S18875
123. Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. *J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi*. 2003;36(4):266-269.
124. Jeong SJ, Lee JU, Song YG, Lee KH, Lee MJ. Delaying diagnostic procedure significantly increases mortality in patients with invasive mucormycosis. *Mycoses*. 2015;58(12):746-752. doi:10.1111/myc.12428
125. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. *J Laryngol Otol*. 2011;125(8):807-810. doi:10.1017/S0022215111001289
126. Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK. Rhinocerebral mucormycosis: the disease spectrum in 27 patients. *Mycoses*. 2007;50(4):290-296. doi:10.1111/j.1439-0507.2007.01364.x

127. Eliashar R, Resnick IB, Goldfarb A, Wohlgelernter J, Gross M. Endoscopic Surgery for Sinonasal Invasive Aspergillosis in Bone Marrow Transplantation Patients. *Laryngoscope*. 2007;117(1):78-81. doi:10.1097/01.mlg.0000245941.03953.5d
128. Taxy JB, El-Zayaty S, Langerman A. Acute Fungal Sinusitis. *Am J Clin Pathol*. 2009;132(1):86-93. doi:10.1309/AJCP9HTH9NRPMYCT
129. Goyal P, Leung MK, Hwang PH. Endoscopic Approach to the Infratemporal Fossa for Treatment of Invasive Fungal Sinusitis. *Am J Rhinol Allergy*. 2009;23(1):100-104. doi:10.2500/ajra.2009.23.3270
130. Langford JD, McCartney DL, Wang RC. Frozen Section-guided Surgical Debridement for Management of Rhino-orbital Mucormycosis. *Am J Ophthalmol*. 1997;124(2):265-267. doi:10.1016/S0002-9394(14)70804-9
131. Zimmermann N, Hagen MC, Schrager JJ, Hebbeler-Clark RS, Masineni S. Utility of frozen section analysis for fungal organisms in soft tissue wound debridement margin determination. *Diagn Pathol*. 2015;10(1):188. doi:10.1186/s13000-015–0423–9
132. Howells RC, Ramadan HH. Usefulness of computed tomography and magnetic resonance in fulminant invasive fungal rhinosinusitis. *Am J Rhinol*. 2001;15(4):255-261.
133. Kasapoglu F, Coskun H, Ozmen OA, Akalin H, Ener B. Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. *Otolaryngol Neck Surg*. 2010;143(5):614-620. doi:10.1016/j.otohns.2010.08.017
134. Prado-Calleros HM, Fajardo-Dolci G, Plowes-Hernández O, Jiménez-Gutiérrez C. [Rhino-Orbital Mucormycosis. Cohort study of its treatment according disease extent and reversion of its pathophysiology]. *Gac Med Mex*. 2016;152(6):770-782.
135. Jiang RS, Hsu CY. Endoscopic Sinus Surgery for Rhinocerebral Mucormycosis. *Am J Rhinol*. 1999;13(2):105-110. doi:10.2500/105065899782106751
136. Plowes Hernández O, Prado Calleros HM, Soberón Marmissolle Daguerre GS, Sadek González A. Rhino-orbito-cerebral mucormycosis. Management strategies to avoid or limit intracraneal affection and improve survival. *Acta Otorrinolaringol Esp*. 2015;66(6):348-352. doi:10.1016/j.otorri.2015.01.007
137. Abu El-Naaj I, Leiser Y, Wolff A, Peled M. The surgical management of rhinocerebral mucormycosis. *J Cranio-Maxillofac Surg*. 2013;41(4):291-295. doi:10.1016/j.jcms.2012.03.019
138. Ketenci İ, Ünlü Y, Kaya H, et al. Rhinocerebral mucormycosis: experience in 14 patients. *J Laryngol Otol*. 2011;125(8):e3. doi:10.1017/S0022215111000843
139. Ramadorai A, Ravi P, Narayanan V. Rhinocerebral mucormycosis: a prospective analysis of an effective treatment protocol. *Ann Maxillofac Surg*. 2019;9(1):192. doi:10.4103/ams.ams_231_18
140. Abedi E, Sismanis A, Choi K, Pastore P. Twenty-Five Years' Experience Treating Cerebro-Rhino-Orbital Mucormycosis. *Laryngoscope*. 1984;94(8):1060-1062. doi:10.1288/00005537-198408000-00013
141. Ardeshirpour F, Bohm LA, Belani KK, Sencer SF, Lander TA, Sidman JD. Surgery for pediatric invasive fungal sinonasal disease: invasive Fungal Sinonasal Disease. *Laryngoscope*. 2014;124(4):1008-1012. doi:10.1002/lary.24369
142. Vironneau P, Kania R, Herman P, et al. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. *Clin Microbiol Infect*. 2014;20(5):O336-O339. doi:10.1111/1469-0691.12408
143. Kolekar JS. Rhinocerebral Mucormycosis: a Retrospective Study. *Indian J Otolaryngol Head Neck Surg*. 2015;67(1):93-96. doi:10.1007/s12070-014–0804–5
144. Valera FCP, do Lago T, Tamashiro E, Yassuda CC, Silveira F, Anselmo-Lima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. *Int J Infect Dis*. 2011;15(12):e841-e844. doi:10.1016/j.ijid.2011.08.005
145. Yakirevitch A, Barg AA, Bedrin L, Primov-Fever A, Wolf M, Migirov L. Acute Invasive Fungal Rhinosinusitis in Children With Hematologic Malignancies: outcome of Surgical Treatment. *Pediatr Hematol Oncol*. 2015;32(8):568-575. doi:10.3109/08880018.2015.1092058
146. Wu P, Huang Y, Yang S, et al. Acute invasive fungal rhinosinusitis in twenty-one diabetic patients. *Clin Otolaryngol*. 2018;43(4):1163-1167. doi:10.1111/coa.13109
147. Kashkouli MB, Abdolalizadeh P, Oghazian M, Hadi Y, Karimi N, Ghazizadeh M. Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. *Br J Ophthalmol*. 2019;103(10):1460-1465. doi:10.1136/bjophthalmol-2018-312688
148. Tarkan Ö, Karagün B, Özdemir S, et al. Endonasal treatment of acute invasive fungal rhinosinusitis in immunocompromised pediatric hematology–oncology patients. *Int J Pediatr Otorhinolaryngol*. 2012;76(10):1458-1464. doi:10.1016/j.ijporl.2012.06.021
149. Vinh D, Yim M, Dutta A, Jones JK, Zhang W, Sitton M. Pediatric invasive fungal rhinosinusitis: an investigation of 17 patients. *Int J Pediatr Otorhinolaryngol*. 2017;99:111-116. doi:10.1016/j.ijporl.2017.05.015
150. Rizk SS, Kraus DH, Gerresheim G, Mudan S. Aggressive combination treatment for invasive fungal sinusitis in immunocompromised patients. *Ear Nose Throat J*. 2000;79(4):278-280, 282, 284–285.
151. Roongrotwattanasiri K, Fooanant S, Naksane L. Invasive fungal rhinosinusitis in Maharaj Nakorn Chiang Mai Hospital. *J Med Assoc Thail Chotmaihet Thangphaet*. 2007;90(11):2524-2528.
152. Vener C, Carrabba M, Fracchiolla NS, et al. Invasive fungal sinusitis: an effective combined treatment in five haematological patients. *Leuk Lymphoma*. 2007;48(8):1577-1586. doi:10.1080/10428190701457923
153. El-Kholy NA, El-Fattah AMA, Khafagy YW. Invasive Fungal Sinusitis in Post COVID -19 Patients: a New Clinical Entity. *Laryngoscope*. 2021;131(12):2652-2658. doi:10.1002/lary.29632
154. Huang YF, Liang KL, Liang CY, Yang PC, Chen JP, Wei LC. Acute Invasive Fungal Rhinosinusitis-Related Orbital Infection: a Single Medical Center Experience. *J Ophthalmol*. 2021;2021:9987871. doi:10.1155/2021/9987871
155. Trief D, Gray ST, Jakobiec FA, et al. Invasive fungal disease of the sinus and orbit: a comparison between mucormycosis and *Aspergillus*. *Br J Ophthalmol*. 2016;100(2):184-188. doi:10.1136/bjophthalmol-2015-306945
156. Pagella F, De Bernardi F, Dalla Gasperina D, et al. Invasive fungal rhinosinusitis in adult patients: our experience in diagnosis and management. *J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg*. 2016;44(4):512-520. doi:10.1016/j.jcms.2015.12.016
157. Ramírez Argueta JJ, Díaz Molina JP, Ortiz Oliva RJ, Carlos Bregni R, Bustamante Y. Resultados de cirugía endoscópica

nasal en el tratamiento de sinusitis fúngica invasiva en niños con cáncer e inmunosupresión. *Acta Otorrinolaringológica Esp*. 2019;70(6):348-357. doi:10.1016/j.otorri.2018.09.001

158. Durand ML, Kitt TM, Song Y, Marty FM. Isavuconazole Treatment of Invasive Fungal Sinusitis: a Post Hoc Analysis of the SECURE and VITAL Trials. *Clin Infect Dis*. 2021;73(6):e1380-e1383. doi:10.1093/cid/ciab386
159. Boyd Gillespie M, Huchton DM, O'Malley BW. Role of Middle Turbinate Biopsy in the Diagnosis of Fulminant Invasive Fungal Rhinosinusitis. *Laryngoscope*. 2000;110(11):1832-1836. doi:10.1097/00005537-200011000-00013
160. Toumi A, Larbi Ammari F, Loussaief C, et al. Rhino-orbito-cerebral mucormycosis: five cases. *Médecine Mal Infect*. 2012;42(12):591-598. doi:10.1016/j.medmal.2012.10.001
161. Hosseini SMS, Borghei P. Rhinocerebral mucormycosis: pathways of spread. *Eur Arch Otorhinolaryngol*. 2005;262(11):932-938. doi:10.1007/s00405-005–0919-0
162. Peterson DE, Schimpff SC. Aspergillus sinusitis in neutropenic patients with cancer : a review. *Biomed Pharmacother*. 1989;43(4):307-312. doi:10.1016/0753–3322(89)90013-9
163. Manesh A, John AO, Mathew B, et al. Posaconazole: an emerging therapeutic option for invasive rhino-orbito-cerebral mucormycosis. *Mycoses*. 2016;59(12):765-772. doi:10.1111/myc.12529
164. Hachem RY, Boktour MR, Hanna HA, et al. Sinus Surgery Combined with Antifungal Therapy is Effective in the Treatment of Invasive Aspergillus Sinusitis in Neutropenic Patients with Cancer. *Infection*. 2008;36(6):539-542. doi:10.1007/s15010-008–7388-5
165. Reed C, Bryant R, Ibrahim AS, et al. Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis. *Clin Infect Dis*. 2008;47(3):364-371. doi:10.1086/589857
166. Siddiqui AA, Shah AA, Bashir SH. Craniocerebral Aspergillosis of Sinonasal Origin in Immunocompetent Patients: clinical Spectrum and Outcome in 25 Cases. *Neurosurgery*. 2004;55(3):602-613. doi:10.1227/01.NEU.0000134597.94269.48
167. Botero Aguirre JP, Restrepo Hamid AM. *Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function*. 2015. doi:10.1002/14651858.CD010481.pub2. Published online November 23.
168. Girmenia C, Cimino G, Di Cristofano F, Micozzi A, Gentile G, Martino P. Effects of hydration with salt repletion on renal toxicity of conventional amphotericin B empirical therapy: a prospective study in patients with hematological malignancies. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2005;13(12):987-992. doi:10.1007/s00520-005–0783-x
169. Branch RA. Prevention of amphotericin B-induced renal impairment. A review on the use of sodium supplementation. *Arch Intern Med*. 1988;148(11):2389-2394.
170. Kyriakidis I, Tragiannidis A, Munchen S, Groll AH. Clinical hepatotoxicity associated with antifungal agents. *Expert Opin Drug Saf*:1-17. doi:10.1080/14740338.2017.1270264. Published online December 16.
171. Levine MT, Chandrasekar PH. Adverse effects of voriconazole: over a decade of use. *Clin Transplant*. 2016;30(11):1377-1386. doi:10.1111/ctr.12834
172. Denning DW. Echinocandin antifungal drugs. *Lancet*. 2003;362(9390):1142-1151. doi:10.1016/S0140-6736(03)14472-8
173. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral Mucormycosis: evolution of the Disease and Treatment Options. *Laryngoscope*. 1997;107(7):855-862. doi:10.1097/00005537-199707000-00004
174. Fung M, Babik J, Humphreys IM, Davis GE. Diagnosis and Treatment of Acute Invasive Fungal Sinusitis in Cancer and Transplant Patients. *Curr Infect Dis Rep*. 2019;21(12):53. doi:10.1007/s11908-019–0707-4
175. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. In Vitro Activities of Posaconazole, Itraconazole, Voriconazole, Amphotericin B, and Fluconazole against 37 Clinical Isolates of Zygomycetes. *Antimicrob Agents Chemother*. 2002;46(5):1581-1582. doi:10.1128/AAC.46.5.1581–1582.2002
176. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016;387(10020):760-769. doi:10.1016/S0140-6736(15)01159-9
177. Maertens JA, Rahav G, Lee DG, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2021;397(10273):499-509. doi:10.1016/S0140-6736(21)00219-1
178. Cornely OA, Maertens J, Bresnik M, et al. Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: a Randomized Trial Comparing a High-Loading Dose Regimen with Standard Dosing (AmBiLoad Trial). *Clin Infect Dis*. 2007;44(10):1289-1297. doi:10.1086/514341
179. Heinz WJ, Buchheidt D, Ullmann AJ. Clinical evidence for caspofungin monotherapy in the first-line and salvage therapy of invasive *Aspergillus* infections. *Mycoses*. 2016;59(8):480-493. doi:10.1111/myc.12477
180. Marr KA, Schlamm HT, Herbrecht R, et al. Combination Antifungal Therapy for Invasive Aspergillosis: a Randomized Trial. *Ann Intern Med*. 2015;162(2):81-89. doi:10.7326/M13-2508
181. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60. doi:10.1093/cid/ciw326
182. Husain S, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9). doi:10.1111/ctr.13544
183. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019;19(12):e405-e421. doi:10.1016/S1473-3099(19)30312-3
184. van Burik JAH, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole Is Effective as Salvage Therapy in Zygomycosis: a Retrospective Summary of 91 Cases. *Clin Infect Dis*. 2006;42(7):e61-e65. doi:10.1086/500212
185. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis*. 2016;16(7):828-837. doi:10.1016/S1473-3099(16)00071-2
186. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of Mucormycosis. *J Fungi*. 2018;4(3):90. doi:10.3390/jof4030090

187. Fung M, Schwartz BS, Doernberg SB, et al. Breakthrough Invasive Fungal Infections on Isavuconazole Prophylaxis and Treatment: what Is Happening in the Real-World Setting? *Clin Infect Dis*. 2018;67(7):1142-1143. doi:10.1093/cid/ciy260
188. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP. Breakthrough Fungal Infections in Patients With Leukemia Receiving Isavuconazole. *Clin Infect Dis*. 2018. doi:10.1093/cid/ciy406. Published online May 16.
189. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect*. 2014;20:27-46. doi:10.1111/1469-0691.12465
190. Rauseo AM, Coler-Reilly A, Larson L, Spec A. Hope on the Horizon: novel Fungal Treatments in Development. *Open Forum Infect Dis*. 2020;7(2):ofaa016. doi:10.1093/ofid/ofaa016
191. Wiederhold NP. Review of the Novel Investigational Antifungal Olorofim. *J Fungi Basel Switz*. 2020;6(3):E122. doi:10.3390/jof6030122
192. Gupta AK, Gupta AK. Postgraduate institute management protocol for invasive Aspergillus flavus sinusitis: is it effective? *Int J Infect Dis*. 2009;13(2):134-139. doi:10.1016/j.ijid.2008.03.035
193. Balai E, Mummadi S, Jolly K, Darr A, Aldeerawi H. Rhinocerebral Mucormycosis: a Ten-Year Single Centre Case Series. *Cureus*. 2020. doi:10.7759/cureus.11776. Published online November 29.
194. Adulkar NG, Radhakrishnan S, Vidhya N, Kim U. Invasive sino-orbital fungal infections in immunocompetent patients: a clinico-pathological study. *Eye*. 2019;33(6):988-994. doi:10.1038/s41433-019–0358-6
195. Baeesa S, Bokhari R, Alghamdi K, Alem H, Al-Maghrabi J, Madani T. Invasive aspergillus sinusitis with orbitocranial extension. *Asian J Neurosurg*. 2014;0(0):0. doi:10.4103/1793–5482.144188
196. Kennedy KJ, Daveson K, Slavin MA, et al. Mucormycosis in Australia: contemporary epidemiology and outcomes. *Clin Microbiol Infect*. 2016;22(9):775-781. doi:10.1016/j.cmi.2016.01.005
197. Sachdeva K. Rhino-oculo Cerebral Mucormycosis with Multiple Cranial Nerve Palsy in Diabetic Patient: review of Six Cases. *Indian J Otolaryngol Head Neck Surg*. 2013;65(4):375-379. doi:10.1007/s12070-013–0659-1
198. Gallien S, Fournier S, Porcher R, et al. Therapeutic Outcome and Prognostic Factors of Invasive Aspergillosis in an Infectious Disease Department: a Review of 34 Cases. *Infection*. 2008;36(6):533-538. doi:10.1007/s15010-008–7375-x
199. Ammari L, Kilani B, Tiouiri H, et al. Mucormycosis: four case reports. *Tunis Med*. 2008;86(2):165-168.
200. Baumann A, Zimmerli S, Häusler R, Caversaccio M. Invasive Sphenoidal Aspergillosis: successful Treatment with Sphenoidotomy and Voriconazole. *ORL*. 2007;69(2):121-126. doi:10.1159/000097858
201. Herbrecht R, Letscher-Bru V, Bowden RA, et al. Treatment of 21 Cases of Invasive Mucormycosis with Amphotericin B Colloidal Dispersion. *Eur J Clin Microbiol Infect Dis*. 2001;20(7):0460-0466. doi:10.1007/s100960100528
202. Kahana A. Use of Radiopaque Intraorbital Catheter in the Treatment of Sino-Orbito-Cranial Mucormycosis. *Arch Ophthalmol*. 2007;125(12):1714. doi:10.1001/archopht.125.12.1714
203. Knipping S, Holzhausen HJ, Koesling S, Bloching M. Invasive aspergillosis of the paranasal sinuses and the skull base. *Eur Arch Otorhinolaryngol*. 2007;264(10):1163-1169. doi:10.1007/s00405-007–0336–7
204. Kohn R, Hepler R. Management of Limited Rhino-orbital Mucormycosis without Exenteration. *Ophthalmology*. 1985;92(10):1440-1444. doi:10.1016/S0161-6420(85)33844-7
205. Bayram N, Ozsaygılı C, Sav H, et al. Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. *Jpn J Ophthalmol*. 2021;65(4):515-525. doi:10.1007/s10384-021-00845-5
206. Luna JD, Ponssa XS, Rodríguez SD, Luna NC, Juárez CP. Intraconal amphotericin B for the treatment of rhino-orbital mucormycosis. *Ophthalmic Surg Lasers*. 1996;27(8):706-708.
207. Seiff SR, Choo PH, Carter SR. Role of Local Amphotericin B Therapy for Sino-Orbital Fungal Infections. *Ophthal Plast Reconstr Surg*. 1999;15(1):28-31. doi:10.1097/00002341-199901000-00007
208. Wakabayashi T, Oda H, Kinoshita N, Ogasawara A, Fujishiro Y, Kawanabe W. Retrobulbar Amphotericin B Injections for Treatment of Invasive Sino-orbital Aspergillosis. *Jpn J Ophthalmol*. 2007;51(4):309-311. doi:10.1007/s10384-007–0437-2
209. Mainville N, Jordan DR. Orbital Apergillosis Treated with Retrobulbar Amphotericin B. *Orbit*. 2012;31(1):15-17. doi:10.3109/01676830.2011.603596
210. Colon-Acevedo B, Kumar J, Richard MJ, Woodward JA. The Role of Adjunctive Therapies in the Management of Invasive Sino-Orbital Infection. *Ophthal Plast Reconstr Surg*. 2015;31(5):401-405. doi:10.1097/IOP.0000000000000488
211. Ashraf DC, Idowu OO, Hirabayashi KE, et al. Outcomes of a Modified Treatment Ladder Algorithm Using Retrobulbar Amphotericin B for Invasive Fungal Rhino-Orbital Sinusitis. *Am J Ophthalmol*. 2022;237:299-309. doi:10.1016/j.ajo.2021.05.025
212. Arreenich P, Saonanon P, Aeumjaturapat S, Snidvongs K, Chusakul S, Kanjanaumporn J. Efficacy and safety of retrobulbar amphotericin B injection in invasive fungal rhinosinusitis with orbital invasion patients. *Rhinol J*. 2021;59(4):387-392. doi:10.4193/Rhin21.070
213. Joos ZP, Patel BCK. Intraorbital Irrigation of Amphotericin B in the Treatment of Rhino-Orbital Mucormycosis. *Ophthal Plast Reconstr Surg*. 2017;33(1):e13-e16. doi:10.1097/IOP.0000000000000377
214. Harris GJ, Will BR. Orbital Aspergillosis: conservative Debridement and Local Amphotericin Irrigation. *Ophthal Plast Reconstr Surg*. 1989;5(3):207-211. doi:10.1097/00002341-198909000-00012
215. Pelton RW, Peterson EA, Patel BCK, Davis K. Successful Treatment of Rhino-orbital Mucormycosis Without Exenteration: the Use of Multiple Treatment Modalities. *Ophthal Plast Reconstr Surg*. 2001;17(1):62-66. doi:10.1097/00002341-200101000-00012
216. Dave TV, Gopinathan Nair A, Hegde R, et al. Clinical Presentations, Management and Outcomes of Rhino-Orbital-Cerebral Mucormycosis (ROCM) Following COVID-19: a Multi-Centric Study. *Ophthal Plast Reconstr Surg*. 2021;37(5):488-495. doi:10.1097/IOP.0000000000002030
217. Sen M, Honavar S, Sengupta S, et al. EpImpact of the use of digital devices on e of COVID-19-associated rhino-orbital-

cerebral mucormycosis in 2826 patients in India – Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC). *Indian J Ophthalmol*. 2021;69(7):1670. doi:10.4103/ijo.IJO_1565_21. Report 1.

218. Hanba C, Svider PF, Lai W, et al. An investigation of operative outcomes: pediatric invasive fungal sinusitis. *Int J Pediatr Otorhinolaryngol*. 2017;102:142-147. doi:10.1016/j.ijporl.2017.09.009
219. Bhattacharyya A, Sarma P, Sharma DJ, et al. Rhino-orbital-cerebral-mucormycosis in COVID-19: a systematic review. *Indian J Pharmacol*. 2021;53(4):317-327. doi:10.4103/ijp.ijp_419_21
220. Hargrove RN, Wesley RE, Klippenstein KA, Fleming JC, Haik BG. Indications for Orbital Exenteration in Mucormycosis. *Ophthal Plast Reconstr Surg*. 2006;22(4):286-291. doi:10.1097/01.iop.0000225418.50441.ee
221. Overall survival and prognostic factors in diabetic patients with invasive fungal rhinosinusitis. *Asian Pac J Allergy Immunol*. Published online 2021. doi:10.12932/AP-310720-0934
222. Berenguer J, Solera J, Moreno S, Muñoz P, Parras F. [Mucormycosis. The disease spectrum in 13 patients]. *Med Clin (Barc)*. 1990;94(20):766-772.
223. Bhadada S, Bhansali A, Reddy KSS, Bhat RV, Khandelwal N, Gupta AK. Rhino-orbital-cerebral mucormycosis in type 1 diabetes mellitus. *Indian J Pediatr*. 2005;72(8):671-674. doi:10.1007/BF02724075
224. Dhiwakar M, Thakar A, Bahadur S. Improving outcomes in rhinocerebral mucormycosis - early diagnostic pointers and prognostic factors. *J Laryngol Otol*. 2003;117(11):861-865. doi:10.1258/002221503322542854
225. Fugate JE. Complications of Neurosurgery. *Contin Lifelong Learn Neurol*. 2015;21:1425-1444. doi:10.1212/CON.0000000000000227
226. Kerezoudis P, Watts CR, Bydon M, et al. Diagnosis and Treatment of Isolated Cerebral Mucormycosis: patient-Level Data Meta-Analysis and Mayo Clinic Experience. *World Neurosurg*. 2019;123:425-434.e5. doi:10.1016/j.wneu.2018.10.218
227. Verma A, Brozman B, Petito CK. Isolated cerebral mucormycosis: report of a case and review of the literature. *J Neurol Sci*. 2006;240(1–2):65-69. doi:10.1016/j.jns.2005.09.010
228. Gupta Mann, Khosla Sastry, Hundal. Original Articles. *Mycoses*. 1999;42(4):225-230. doi:10.1046/j.1439-0507.1999.00470.x
229. Ma J, Jia R, Li J, et al. Retrospective clinical study of eighty-one cases of intracranial mucormycosis. *J Glob Infect Dis*. 2015;7(4):143. doi:10.4103/0974-777X.170497
230. Immune response to fungi in diabetic patients with invasive fungal rhinosinusitis. *Asian Pac J Allergy Immunol*. Published online 2020. doi:10.12932/AP-080620-0874
231. Goering P, Berlinger NT, Weisdorf DJ. Aggressive combined modality treatment of progressive sinonasal fungal infections in immunocompromised patients. *Am J Med*. 1988;85(5):619-623.
232. Casadevall A, Pirofski L. Adjunctive Immune Therapy for Fungal Infections. *Clin Infect Dis*. 2001;33(7):1048-1056. doi:10.1086/322710
233. Humphreys IM, Wandell GM, Miller C, et al. A multi-institutional review of outcomes in biopsy-proven chronic invasive fungal sinusitis. *Int Forum Allergy Rhinol*. 2020;10(6):738-747. doi:10.1002/alr.22547
234. Zappasodi P, Rossi M, Castagnola C, et al. Resolution of invasive fungal sinusitis in immunocompromised patients: neutrophil count is crucial beside a combined medical and surgical approach. *Ann Hematol*. 2010;89(7):737-739. doi:10.1007/s00277-009–0854-z
235. Wan L, Zhang Y, Lai Y, et al. Effect of Granulocyte-Macrophage Colony-Stimulating Factor on Prevention and Treatment of Invasive Fungal Disease in Recipients of Allogeneic Stem-Cell Transplantation: a Prospective Multicenter Randomized Phase IV Trial. *J Clin Oncol*. 2015;33(34):3999-4006. doi:10.1200/JCO.2014.60.5121
236. Sam QH, Yew WS, Seneviratne CJ, Chang MW, Chai LYA. Immunomodulation as Therapy for Fungal Infection: are We Closer? *Front Microbiol*. 2018;9:1612. doi:10.3389/fmicb.2018.01612
237. West KA, Gea-Banacloche J, Stroncek D, Kadri SS. Granulocyte transfusions in the management of invasive fungal infections. *Br J Haematol*. 2017;177(3):357-374. doi:10.1111/bjh.14597
238. Nagai H, Guo J, Choi H, Kurup V. Interferon- and Tumor Necrosis Factor- Protect Mice from Invasive Aspergillosis. *J Infect Dis*. 1995;172(6):1554-1560. doi:10.1093/infdis/172.6.1554
239. The International Chronic Granulomatous Disease Cooperative Study Group*. A Controlled Trial of Interferon Gamma to Prevent Infection in Chronic Granulomatous Disease. *N Engl J Med*. 1991;324(8):509-516. doi:10.1056/NEJM199102213240801
240. Marciano BE, Wesley R, De Carlo ES, et al. Long-Term Interferon- Therapy for Patients with Chronic Granulomatous Disease. *Clin Infect Dis*. 2004;39(5):692-699. doi:10.1086/422993
241. Armstrong-James D, Teo IA, Shrivastava S, et al. Exogenous Interferon-γ Immunotherapy for Invasive Fungal Infections in Kidney Transplant Patients: iFN-γ for Invasive Fungal Infections. *Am J Transplant*. 2010;10(8):1796-1803. doi:10.1111/j.1600–6143.2010.03094.x
242. Perruccio K, Tosti A, Burchielli E, et al. Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. *Blood*. 2005;106(13):4397-4406. doi:10.1182/blood-2005–05-1775
243. Kumaresan PR, Manuri PR, Albert ND, et al. Bioengineering T cells to target carbohydrate to treat opportunistic fungal infection. *Proc Natl Acad Sci*. 2014;111(29):10660-10665. doi:10.1073/pnas.1312789111
244. Morrison VA, McGlave PB. Mucormycosis in the BMT population. *Bone Marrow Transplant*. 1993;11(5):383-388.
245. Tzelnick S, Soudry E. Rhinosinusitis in Solid Organ Transplant Recipients: analysis of 4562 Transplanted Patients. *Am J Rhinol Allergy*. 2019;33(1):56-61. doi:10.1177/1945892418808717
246. Kohashi S, Toyama T, Hashimoto N, et al. Sinusitis caused by *Exserohilum rostratum* after cord blood transplantation for myelodysplastic syndrome: a case report and literature review. *Transpl Infect Dis*. 2018;20(1):e12805. doi:10.1111/tid.12805
247. Choi SS, Milmoe GJ, Dinndorf PA, Quinones RR. Invasive Aspergillus Sinusitis in Pediatric Bone Marrow Transplant Patients: evaluation and Management. *Arch Otolaryngol - Head Neck Surg*. 1995;121(10):1188-1192. doi:10.1001/archotol.1995.01890100092016

248. Ismaiel WF, Abdelazim MH, Eldsoky I, et al. The impact of COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. *Am J Otolaryngol*. 2021;42(6):103080. doi:10.1016/j.amjoto.2021.103080
249. Ravani S, Agrawal G, Leuva P, Modi P, Amin K. Rise of the phoenix: mucormycosis in COVID-19 times. *Indian J Ophthalmol*. 2021;69(6):1563. doi:10.4103/ijo.IJO_310_21
250. Burton BN, Jafari A, Asmerom B, Swisher MW, Gabriel RA, DeConde A. Inpatient Mortality After Endoscopic Sinus Surgery for Invasive Fungal Rhinosinusitis. *Ann Otol Rhinol Laryngol*. 2019;128(4):300-308. doi:10.1177/0003489418820871
251. Shintani-Smith S, Luong AU, Ramakrishnan VR, Tan BK, French DD, Kern RC. Acute invasive fungal sinusitis: epidemiology and outcomes in the United States. *Int Forum Allergy Rhinol*. 2022;12(2):233-236. doi:10.1002/alr.22896
252. Al-Obaidi M, Youssefi B, Bardwell J, Bouzigard R, Le CH, Zangeneh TT. A Comparative Analysis of Mucormycosis in Immunosuppressed Hosts Including Patients with Uncontrolled Diabetes in the Southwest United States. *Am J Med*. 2021;134(9):1155-1159. doi:10.1016/j.amjmed.2021.04.008
253. Nussbaum ES, Hall WA. Rhinocerebral mucormycosis: changing patterns of disease. *Surg Neurol*. 1994;41(2):152-156. doi:10.1016/0090–3019(94)90114-7
254. Otto KJ, DelGaudio JM. Invasive Fungal Rhinosinusitis: what is the Appropriate Follow-Up? *Am J Rhinol*. 2006;20(6):582-585. doi:10.2500/ajr.2006.20.2946
255. Shirazi MA, Stankiewicz JA, Kammeyer P. Activity of Nasal Amphotericin B Irrigation against Fungal Organisms *in Vitro*. *Am J Rhinol*. 2007;21(2):145-148. doi:10.2500/ajr.2007.21.2988
256. Ashour MM, Abdelaziz TT, Ashour DM, Askoura A, Saleh MI, Mahmoud MS. Imaging spectrum of acute invasive fungal rhino-orbital-cerebral sinusitis in COVID-19 patients: a case series and a review of literature. *J Neuroradiol*. 2021;48(5):319-324. doi:10.1016/j.neurad.2021.05.007
257. Hong HL, Lee YM, Kim T, et al. Risk Factors for Mortality in Patients with Invasive Mucormycosis. *Infect Chemother*. 2013;45(3):292. doi:10.3947/ic.2013.45.3.292

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